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THÈSE DE DOCTORAT

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Stratégies d'amélioration de la prise en charge des patients souffrants de premiers épisodes psychotiques

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Composition du jury

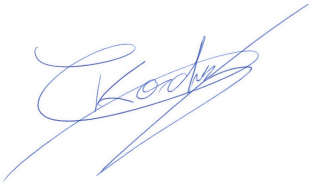
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Liste de publications et/ou brevets et participation aux conférences

1) Liste des publications et/ou brevet [1] réalisées dans le cadre du projet de thèse :

1. “Sexual Dysfunction in Schizophrenia: A Systematic Review and Meta-Analysis” JAMA PSYCHIATRY 2023. T Korchia et al. DOI: 10.1001/jamapsychiatry.2023.2696

2. “Precision-medicine findings from the FACE-SZ cohort to develop motivation-enhancing programs in real-world schizophrenia”. WORLD JOURNAL OF BIOLOGICAL PSYCHIATRY 2022. T Korchia et al. DOI: 10.1080/15622975.2022.2031286

3. “Collaborative discontinuation of antipsychotics after the first episode of psychosis”. JOURNAL OF PSYCHIATRY AND NEUROSCIENCES 2023. T Korchia et al. DOI: 10.1503/220223

4. “Utilizing pharmacogenetics when treating first episode psychosis”. JOURNAL OF PSYCHIATRY AND NEUROSCIENCES 2023. T Korchia et al. DOI: 10.1503/jpn.220154

5. “Towards Precision Dosing of Clozapine in Schizophrenia: External Evaluation of Population Pharmacokinetic Models and Bayesian Forecasting”. Therapeutic Drug Monitoring 2022. A Lereclus, T Korchia et al. DOI: 10.1097/FTD.0000000000000987

6. Soumission dans l’encéphale 2023 : “UM CYP450 metabolizers are at higher risk of suicide attempts in schizophrenia” T. KORCHIA et al

[1] Cette liste comprend les articles publiés, les articles soumis à publication et les articles en préparation ainsi que les livres, chapitres de livre et/ou toutes formes de valorisation des résultats des travaux propres à la discipline du projet de thèse. La référence aux publications doit suivre les règles standards de bibliographie et doit être conforme à la charte des publications d’AMU.

2) Participation aux conférences[2] et écoles d'été au cours de la période de thèse :

1. Congrès mondial sur la schizophrénie par la société internationale de recherche sur la schizophrénie en 2023 à Toronto (Présentation et poster. Award meilleur jeune carrière de recherche sur la schizophrénie)

2. Colloque McGill Montréal 2022 : présentation des travaux sur l'impact de la motivation dans la schizophrénie

3. Congrès Français de psychiatrie 2023

4. Congrès de l'Encéphale 2024

5. Rencontres internationales sur la schizophrénie 2023 : présentation orale de l'importance de la prise en charge des effets indésirables sexuels

6. Congrès annuel de l'association des psychiatres candaiens 2022

7. Rencontre nationale de sexologie : présentation sur l'importance des dysfonctions sexuelles dans la schizophrénie

[2] Le terme « conférence » est générique. Il désigne à la fois « conférence », « congrès », « workshop », « colloques », « rencontres nationales et/ou internationales » … etc.
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Résumé

La prise en charge des premiers épisodes psychotiques représente un défi clinique et thérapeutique majeur.
Nous avons exploré plusieurs axes pour une approche plus efficace et personnalisée : la pharmacogénétique, la motivation du patient, les dysfonctions sexuelles, et la durée du traitement antipsychotique.

L'interdépendance de ces éléments souligne certains aspects importants de la psychiatrie actuelle. Pour appréhender efficacement les troubles schizophréniques débutants, une stratégie multidimensionnelle est indispensable.

L'étude de la pharmacogénétique permet de souligner l'importance de la personnalisation du traitement pharmacologique. Cette discipline optimise le choix du traitement antipsychotique tout en minimisant les risques d'effets indésirables. Cette démarche pose les bases d'une prise en charge personnalisée. L'identification précoce des patients à risque de non-réponse à certains médicaments ou susceptibles de développer des effets secondaires graves comme le risque accru de suicide renforce la nécessité de cette approche.
Nous avons aussi vu comment les prescriptions précoces de clozapine pourraient concourir à une amélioration globale de la prise en charge des premiers épisodes, notamment via une réduction des idées suicidaires.

La motivation du patient, au cœur du syndrome négatif, est un élément clé pour sa qualité de vie. Un patient informé et impliqué dans les décisions thérapeutiques est plus à même de s'engager dans le processus de guérison. La pharmacogénétique, en offrant des options thérapeutiques personnalisées, peut donc augmenter le sentiment d'empowerment du patient. Ce lien entre la personnalisation du traitement et la motivation du patient est crucial, car une adhésion optimale au traitement est souvent le pilier d'un pronostic favorable et d'une alliance thérapeutique de qualité. La motivation est également renforcée par le soutien psychosocial et les stratégies thérapeutiques ciblées, soulignant là encore l'importance d'une prise en charge globale.

Les dysfonctions sexuelles, fréquemment rencontrées chez les patients atteints de troubles schizophréniques, constituent un obstacle majeur à la qualité de vie et à l'acceptation du traitement. Cette problématique est aussi liée à la pharmacogénétique (notamment avec la prévention des effets indésirables sexuels) avec un impact direct sur la motivation. Les effets secondaires des antipsychotiques, pouvant inclure des dysfonctions sexuelles, mettent en lumière le besoin d'une sélection soignée des médicaments, basée sur le profil génétique du patient.

La décision concernant la durée du traitement et son arrêt ne peut être prise isolément par le psychiatre, mais doit considérer les aspects pharmacogénétiques, la motivation et le bien-être global du patient, y compris sa vie sexuelle. Une approche flexible et personnalisée, ajustant la durée du traitement en fonction des besoins spécifiques et des préférences du patient, peut renforcer l'alliance thérapeutique et l'adhésion au traitement à long terme. Cette flexibilité, loin d'être un signe d'incertitude, reflète une compréhension approfondie des nuances de la prise en

charge psychiatrique, où le patient est véritablement au cœur du processus décisionnel.

En conclusion, la prise en charge des premiers épisodes psychotiques dans les troubles schizophréniques nécessite une approche intégrée et personnalisée, où la pharmacogénétique, la motivation du patient, la gestion des dysfonctions sexuelles, et la flexibilité de la durée des traitements sont envisagées comme un tout cohérent.
Ce n'est qu'en reconnaissant et en adressant l'interconnexion entre ces divers aspects que nous pouvons aspirer à une prise en charge efficace et respectueuse des besoins uniques de chaque patient. Cette vision holistique est essentielle pour avancer vers une psychiatrie plus humaine et personnalisée, capable de répondre de manière optimale aux défis posés par la prise en charge des premiers épisodes psychotiques.

Abstract

The management of first episodes of psychosis represents a major clinical and therapeutic challenge.
We have explored several avenues for a more effective and personalised approach: pharmacogenetics, patient motivation, sexual dysfunction and the duration of antipsychotic treatment.

The interdependence of these elements highlights certain important aspects of current psychiatry. A multi-dimensional strategy is essential if we are to deal effectively with schizophrenic disorders in their early stages.

The study of pharmacogenetics highlights the importance of personalising pharmacological treatment. This discipline optimises the choice of antipsychotic treatment while minimising the risk of adverse effects. This approach lays the foundations for personalised care. The early identification of patients at risk of non-response to certain drugs or likely to develop serious side-effects such as an increased risk of suicide reinforces the need for this approach.
We have also seen how early prescriptions of clozapine could contribute to an overall improvement in the management of first episodes, particularly through a reduction in suicidal ideation.

Patient motivation, at the heart of the negative syndrome, is a key factor in quality of life. An informed patient who is involved in therapeutic decisions is more likely to commit to the recovery process. Pharmacogenetics, by offering personalised therapeutic options, can therefore increase patients' sense of empowerment. This link between personalised treatment and patient motivation is crucial, as optimal adherence to treatment is often the cornerstone of a favourable prognosis and a high-quality therapeutic alliance. Motivation is also enhanced by psychosocial support and targeted therapeutic strategies, underlining once again the importance of comprehensive care.

Sexual dysfunction, frequently encountered in patients with schizophrenic disorders, is a major obstacle to quality of life and acceptance of treatment. This problem is also linked to pharmacogenetics (in particular the prevention of undesirable sexual effects), with a direct impact on motivation. The side effects of antipsychotics, which can include sexual dysfunction, highlight the need for careful selection of drugs, based on the patient's genetic profile.

Decisions about the duration of treatment and its discontinuation cannot be taken in isolation by the psychiatrist, but must take account of pharmacogenetic aspects, motivation and the patient's overall well-being, including his or her sex life. A flexible, personalised approach, adjusting the duration of treatment according to the patient's specific needs and preferences, can strengthen the therapeutic alliance and long-term adherence to treatment. This flexibility, far from being a sign of uncertainty, reflects a thorough understanding of the nuances of psychiatric care, where the patient is truly at the heart of the decision-making process.

In conclusion, the management of first-episode psychosis in schizophrenia requires an integrated and personalised approach, in which pharmacogenetics, patient

motivation, management of sexual dysfunction and flexibility in the duration of treatment are considered as a coherent whole.
It is only by recognising and addressing the interconnection between these various aspects that we can aspire to effective management that respects the unique needs of each patient. This holistic vision is essential if we are to move towards a more humane and personalised psychiatry, capable of providing an optimal response to the challenges posed by the management of first episodes of psychosis.

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Introduction

A Troubles schizophréniques évolution et pronostic : intérêt d'une prise en charge précoce

Les troubles schizophréniques touchent environ **1% de la population**(1), et débutent classiquement entre 15 et 25 ans(2). Il s'agit d'un trouble psychiatrique complexe, définit dans les principales classifications internationales des maladies, telles que le Manuel diagnostique et statistique des troubles mentaux (DSM) et la Classification internationale des maladies (CIM).

Selon le **DSM-5**, publié par l'Association américaine de psychiatrie, les troubles schizophréniques se caractérise par des symptômes tels que des hallucinations, des délires, un discours désorganisé, un comportement catatonique ou significativement désorganisé, et des symptômes négatifs, comme un appauvrissement affectif ou un manque de volonté (3).
La **CIM-11**, élaborée par l'Organisation mondiale de la santé classifie des critères diagnostiques qui sont similaires(4), tout en soulignant l'importance des dysfonctionnements dans les domaines du travail, des relations interpersonnelles ou du soin de soi.

Les troubles schizophréniques sont des troubles aux manifestations diverses, impliquant des perturbations profondes dans la cognition, l'émotion et le comportement, qui affectent de manière importante la vie quotidienne du patient(5).

Ces troubles sont invalidants, et le pronostic et l'espérance de vie reste particulièrement sombre. Une méta analyse récente (6) a ainsi montré que les individus atteints de troubles schizophréniques meurent prématurément, avec une espérance de vie réduite de 15 à 20 ans par rapport à la population générale. Cette étude montre que le risque de mortalité toutes causes confondues est plus de deux fois supérieur chez les personnes atteintes de troubles schizophréniques par rapport à des groupes de contrôle non atteints (RR=2.52). Les risques de mortalité varient selon les phases de la maladie et sont particulièrement élevés au début des troubles. Les personnes souffrantes de troubles schizophréniques à un stade précoce de la maladie (premiers épisodes psychotiques) présentent un risque encore plus élevé (RR=7.43 pour les premiers épisodes et RR=3.52 pour les troubles schizophréniques incidents)(6). La prise en charge des phases précoces des troubles est importante car un retard diagnostique peut aggraver l'évolution et le devenir des patients(7). Ces données soulignent l'importance d'une prise en charge précoce et multidisciplinaire (8) pour les personnes atteintes de troubles schizophréniques, en mettant l'accent sur la prévention et le traitement des comorbidités(9).

Par ailleurs, les personnes atteintes de troubles schizophréniques font face à une morbidité élevée liée à divers facteurs tels que l'usage de substances(10), un mode de vie sédentaire(11), l'isolement (12) et les effets secondaires des médicaments(13), contribuant à une surmortalité(14). L'absence de suivi médical de ces patients sur le plan somatique et la stigmatisation importante de cette pathologie (15) sont autant de freins à la prise en charge globale et optimale de ces patients (16).
Ce constat alarmant souligne l'importance d'une prise en charge efficace et intégrée des troubles schizophréniques, non seulement en termes de traitements psychiatriques, mais aussi en ce qui concerne la santé physique des patients.

Au cours de ce travail de thèse, nous nous nous sommes plus particulièrement intéressés au **début des troubles psychotiques** et à leurs prises en charge médicamenteuse, bien qu'il soit le plus souvent difficile de faire la distinction entre le premier épisode et la phase initiale des troubles.

B- Détection précoce : entre premier épisode et psychose débutante

La détection précoce des premiers épisodes psychotiques est souvent difficile(17), principalement en raison de la nature insidieuse du début des troubles. Dans la moitié des cas, la symptomatologie débute par des symptomes positifs (avec hallucinations et délires) francs qui conduisent le plus souvent aux urgences psychiatriques(18). Mais ce mode d'apparition brutal n'est pas pour autant le seul mode d'entre dans la maladie. En effet, dans 50% des cas, les premiers signes sont des symptômes négatifs, tels que le retrait social, la diminution de l'expression émotionnelle ou l'apathie. Ces symptômes sont souvent subtils et peuvent facilement être confondus avec ceux d'une dépression (19) ou d'autres troubles mentaux moins sévères, ou parfois même être considérés comme des comportements adolescents typiques. Cela retarde souvent la reconnaissance des troubles et par conséquent, le début du traitement approprié.

Les troubles psychotiques évoluent avec le temps dans leurs présentations cliniques et se manifestent différemment d'un individu à l'autre. Enfin, la stigmatisation associée à la maladie mentale (15) et, en particulier à la psychose, se révèle souvent être un frein pour les individus et leurs familles de chercher de l'aide. Les symptômes initiaux, souvent interprétés comme un comportement anormal ou antisocial, peuvent alors être cachés ou minimisés. Cette stigmatisation peut également influencer la manière dont les symptômes sont perçus et gérés par les professionnels de santé, entravant potentiellement un diagnostic et un traitement précoces.

Repérer et prendre en charge précocement ces situations cliniques est un processus parfois difficile(20). Les professionnels de santé doivent évaluer soigneusement les symptômes, souvent subtils ou atypiques au début, tout en distinguant les troubles schizophréniques des autres troubles psychiatriques. La mise en œuvre d'interventions précoces est aussi complexe (21)en pratique et requiert des équipes spécialisées(22). Il convient en effet de savoir repérer rapidement certains symptomes sans créer une anxiété importante dont on sait qu'elle peut être à la fois un frein à la qualité de vie, mais également un frein à la compliance à un traitement éventuel.

Malgré ces défis, il est essentiel de reconnaître et de traiter les troubles schizophréniques dès les premiers stades. Des études montrent que **plus le traitement est initié tôt après l'apparition des premiers symptômes, meilleur est le pronostic à long terme pour le patient** (23). Une intervention précoce peut limiter la sévérité des symptômes, améliorer la qualité de vie, et réduire les répercussions sur le fonctionnement social et professionnel(24). Elle peut également diminuer la probabilité de rechutes et d'autres complications associées aux troubles schizophréniques.

Par conséquent, malgré les difficultés inhérentes à la gestion des premiers épisodes psychotiques, leur identification et leur traitement précoces sont des éléments majeurs pour améliorer l'évolution à long terme des patients atteints de troubles schizophréniques(25). C'est pour cette raison que nous avons choisi de focaliser notre travail sur la **prise en charge** précoce de ces patients.

C- Traitement des premiers épisodes psychotiques et pharmacogénétique

Les traitements antipsychotiques constituent l'une des principales stratégies dans la prise en charge des troubles schizophréniques(26).

L'utilisation d'antipsychotiques au cours des premiers épisodes, en particulier les antipsychotiques de seconde génération, est associée à une réduction de la mortalité (RR=0.71 pour l'usage d'antipsychotiques en général, avec des effets plus marqués pour certains types)(6).
Cependant, les antipsychotiques sont pourvoyeurs d'effets secondaires parfois importants, renforçant la morbidité et la mortalité chez les personnes souffrant de troubles schizophréniques(27).

L'acceptation des traitements psychotropes par les patients, en particulier jeunes, ainsi que la gestion de leurs effets secondaires constituent donc un défi pour les cliniciens(28).

Une gestion thérapeutique adaptée et personnalisée, favorisant les traitements les plus efficaces et les moins risqués pour chaque patient doit être systématiquement recherchée. La méta analyse de Correll et al. (6) a mis en

lumière que la **diminution de l'espérance de vie** (notamment en lien avec le suicide) dans les troubles schizophréniques semble être améliorable en ciblant davantage le traitement antipsychotique de seconde génération à un stade précoce notamment, et l'utilisation de la clozapine.

La pharmacogénétique constitue l'un des moyens permettant une **prise en charge** individualisée du traitement pharmacologique des patients souffrants de troubles schizophréniques(29). Elle étudie l'influence des variations génétiques sur la réponse aux médicaments, et joue donc un rôle déterminant dans la personnalisation du traitement des patients. Cette approche doit permettre d'adapter les traitements en fonction du profil génétique individuel, améliorant ainsi l'efficacité des médicaments antipsychotiques tout en minimisant les effets secondaires potentiels(30).
De nombreuses études ont montré que certaines variations génétiques peuvent affecter le métabolisme des médicaments, leur transport, leur cible et leur réponse, influençant ainsi la tolérance et l'efficacité du traitement(31). Par exemple, les variations des gènes CYP450, peuvent prédire la réponse aux antipsychotiques et prévenir des effets secondaires graves(32).
En intégrant progressivement la pharmacogénétique dans la gestion thérapeutique, les cliniciens peuvent mieux identifier quels patients bénéficieront de certains antipsychotiques ou nécessiteront des ajustements posologiques. Cela devrait permettre de renforcer à la fois l'alliance thérapeutique en intégrant le patient dans la démarche de soins, mais également de **renforcer sa motivation** (symptôme clé dans le syndrome négatif). De nombreux patients sont en effets inquiets des effets indésirables qui affectent à la fois leurs santés physiques, mais également leurs espoirs d'une stabilité clinique sans effet indésirable.

Malgré son intérêt, l'intégration de la pharmacogénétique dans la pratique clinique quotidienne pour le traitement des troubles schizophréniques présente des défis et soulève des questionnements pour de nombreux psychiatres(33).

L'un des principaux obstacles est le besoin de ressources et d'expertise pour interpréter les résultats des tests génétiques et les traduire en stratégies thérapeutiques concrètes. De plus, les études pharmacogénétiques dans les troubles schizophréniques sont souvent limitées par la taille des échantillons et la diversité des populations étudiées, ce qui peut rendre difficile la généralisation des résultats.
Cependant, avec l'avancée des technologies de séquençage génétique et l'accroissement des connaissances sur les variations génétiques associées à la réponse aux antipsychotiques, la pharmacogénétique doit permettre dans l'avenir de mieux adapter les traitements psychotropes. Ces techniques peuvent être actuellement utilisées en routine clinique, c'est ce que nous avons voulu montrer dans une première publication(34).

D- Impact de la motivation et de l'engagement dans la prise en charge

La motivation affecte de manière significative le fonctionnement quotidien et la qualité de vie des personnes atteintes de troubles schizophréniques(35). Les déficits de motivation aggravent les symptômes négatifs, ce qui peut conduire à un retrait social, une diminution de l'activité physique, et un désintérêt pour les activités quotidiennes. Ces changements comportementaux ont un impact direct sur la capacité d'une personne à travailler, à entretenir des relations sociales et à gérer les activités de la vie quotidienne(36). Un manque de motivation peut également augmenter le sentiment d'isolement et aggraver les symptômes dépressifs, créant un cercle vicieux qui peut rendre la gestion de la maladie encore plus difficile.
La motivation est également un facteur clé dans le **rétablissement** et la réhabilitation des personnes atteintes de troubles schizophréniques(37). Le renforcement de la motivation peut aider les patients à s'engager activement dans leur traitement, y compris la thérapie comportementale, les interventions psychosociales, et la gestion des médicaments. Une motivation accrue est liée à une meilleure adhésion au traitement, à une participation plus active aux activités thérapeutiques, et à une plus grande ouverture à l'apprentissage de compétences sociales et de stratégies d'adaptation. Par conséquent, travailler sur la motivation, notamment sociale, dès les premières phases des troubles schizophréniques est essentiel pour améliorer non seulement les résultats cliniques, mais également pour soutenir une intégration sociale et professionnelle réussie(38).

Dans les premières phases des troubles schizophréniques, la motivation pourrait donc jouer un rôle important pour **l'observance** dans le traitement**.** En effet, les symptômes négatifs des troubles schizophréniques, tels que le manque de motivation ou l'apathie, sont souvent parmi les premiers signes de la maladie, et leurs prises en charge est capitale(36). Ils peuvent affecter de manière significative la capacité d'un individu à reconnaître la nécessité d'une aide médicale et à rechercher activement un traitement. Cette diminution de la motivation peut conduire à un retard dans le diagnostic et l'initiation du traitement. C'est donc un problème important car nous avons vu qu'une intervention précoce est associée à de meilleurs résultats à long terme.
En outre, un manque de motivation pourrait entraver l'adhésion au traitement(39), élément clé pour gérer efficacement les symptômes et prévenir les rechutes.

E- Lien entre Motivation et Dysfonctions Sexuelles

Les dysfonctions sexuelles, fréquemment observées chez les patients atteints de troubles schizophréniques, peuvent avoir un impact significatif sur la motivation et l'estime de soi(40). L'étude que nous avons conduite a mis en évidence la très haute prévalence des effets indésirables sexuels chez ces

patients, souvent jeunes, âgés de 15 à 25 ans(41). Cette prévalence élevée de dysfonctions sexuelles peut entraîner une détérioration de l'estime de soi, aggravant ainsi les déficits de motivation déjà présents dans les troubles schizophréniques(42). Ces problèmes peuvent non seulement affecter le bien-être émotionnel et psychologique des patients, mais aussi leur adhérence au traitement et leur engagement dans les interventions thérapeutiques, rendant la gestion des épisodes psychotiques débutants plus complexe.

Une meilleure compréhension des dysfonctions sexuelles dans les troubles schizophréniques est d'une importance majeure pour améliorer la prise en charge des épisodes psychotiques débutants(43). En reconnaissant et en traitant ces dysfonctions, les professionnels de santé peuvent aider à restaurer l'estime de soi des patients et, par conséquent, renforcer leur motivation à s'engager dans le traitement. Cela est particulièrement crucial chez les patients jeunes, pour qui les problèmes sexuels sont particulièrement perturbants et stigmatisants. En intégrant la gestion des dysfonctions sexuelles dans les programmes de traitement des troubles schizophréniques, notamment lors des premiers épisodes, on peut espérer améliorer non seulement les symptômes de la maladie, mais aussi la qualité de vie globale des patients(44), facilitant ainsi leur rétablissement et leur réintégration sociale.

F- Arrêt des antipsychotiques dans les premiers épisodes psychotiques

Le manque de motivation et les effets indésirables des médicaments sont deux raisons pour lesquelles de nombreux patients souffrant de troubles schizophréniques envisagent d'arrêter leur traitement(45). Ces défis sont particulièrement préoccupants car ils peuvent compromettre l'efficacité du traitement et la qualité de vie des patients(46). Le manque de motivation, souvent exacerbé par les symptômes négatifs des troubles schizophréniques tels que l'apathie et le retrait social, peut réduire la capacité du patient à adhérer à un régime thérapeutique complexe. En outre, les effets indésirables des médicaments antipsychotiques, qui peuvent inclure des effets secondaires comme la prise de poids, les dyskinésies tardives, et la somnolence, peuvent être si pénibles que les patients préfèrent risquer une rechute de leurs symptômes psychotiques plutôt que de continuer à souffrir de ces conséquences indésirables.

Face à ces défis, il est important que les psychiatres accompagnent le souhait des patients de cesser leur traitement, en particulier durant les premiers épisodes psychotiques(47). Une prise en charge attentive et personnalisée peut aider à établir un rapport de confiance entre le patient et le soignant, essentiel pour encourager l'adhésion au traitement à long terme. En outre, une évaluation minutieuse des raisons souhaitant l'arrêt du traitement permet d'ajuster les médicaments pour minimiser les effets indésirables, tout en préservant leur efficacité. C'est particulièrement crucial durant les premiers épisodes psychotiques, où un traitement efficace et bien toléré peut significativement

influencer le pronostic à long terme de la maladie, réduisant le risque de rechutes futures et améliorant l'intégration sociale et professionnelle du patient. Ainsi, en prenant en compte et en gérant soigneusement les préoccupations des patients concernant leur traitement, les psychiatres peuvent jouer un rôle clé dans le soutien de la récupération et de la qualité de vie des personnes souffrant de troubles schizophréniques(48).

Chapitre 1 : La pharmacogénétique dans les premiers épisodes psychotiques

A- Pharmacodynamie, pharmacocinétique et pharmacogénétique

B- Les cytochromes P450

C- Pharmacogénétique et premiers épisodes psychotique (***Utilizing pharmacogenetics when treating first episode psychosis***)

D- Le risque suicidaire en fonction du métabolisme (**UM CYP450 metabolizers are at higher risk of suicide attempts in schizophrenia**)

E- Pharmacogénétique et clozapine dans les premiers épisodes psychotiques (**Towards Precision Dosing of Clozapine in Schizophrenia: External Evaluation of Population Pharmacokinetic Models and Bayesian Forecasting**)

A- Pharmacodynamie, pharmacocinétique et pharmacogénétique :

La pharmacogénétique est un champ de recherche en pleine expansion. Son intérêt dans l'adaptation des traitements dans les troubles schizophréniques débutants est un enjeu important de la recherche(49). Les variations génétiques individuelles pourraient influencer la réponse aux médicaments(50), et c'est tout l'enjeu des prises en charges à la fois personnalisées et précoces(51).

La pharmacodynamie et la pharmacocinétique sont deux branches fondamentales de la pharmacologie. La pharmacodynamie s'intéresse à l'effet des médicaments sur l'organisme, tandis que la pharmacocinétique étudie comment l'organisme utilise les médicaments, en termes d'absorption, de distribution, de métabolisme et d'élimination. La pharmacogénétique, quant à elle, se concentre sur l'impact des variations génétiques sur ces deux processus. Elle vise à comprendre comment les différences génétiques entre individus peuvent affecter leur réponse à un médicament, tant en termes d'efficacité que de sécurité.

L'impact des médicaments sur l'organisme est modulé par des facteurs pharmacocinétiques, qui dictent la distribution sanguine et l'efficacité moléculaire de ces agents thérapeutiques. Ces éléments sont cruciaux pour comprendre le modèle pharmacocinétique-pharmacodynamique (PK-PD), qui fusionne ces deux branches pour prévoir l'effet d'un médicament sous diverses circonstances.

La **pharmacocinétique (PK)** analyse donc le cheminement d'un médicament au sein de l'organisme, de son introduction à son élimination. Elle lie la quantité de médicament donnée aux niveaux détectés dans le sang au fil du temps, offrant un cadre pour comprendre la dynamique du médicament.

Le parcours d'un médicament dans l'organisme se déroule en quatre étapes essentielles :

1- **Absorption** : L'entrée du médicament dans la circulation sanguine depuis son point d'administration. Par exemple, les antipsychotiques oraux sont initialement métabolisés dans le foie avant d'atteindre le reste de l'organisme.

2- **Distribution** : La diffusion du médicament à travers les divers tissus, avec une affinité particulière pour les tissus ciblés. Les molécules lipophiles, telles que les antipsychotiques, ont tendance à s'accumuler dans les tissus gras, y compris le cerveau, qui est souvent la cible visée.

3- **Métabolisme** : La transformation du médicament en métabolites par les processus enzymatiques, souvent par l'intermédiaire des cytochromes

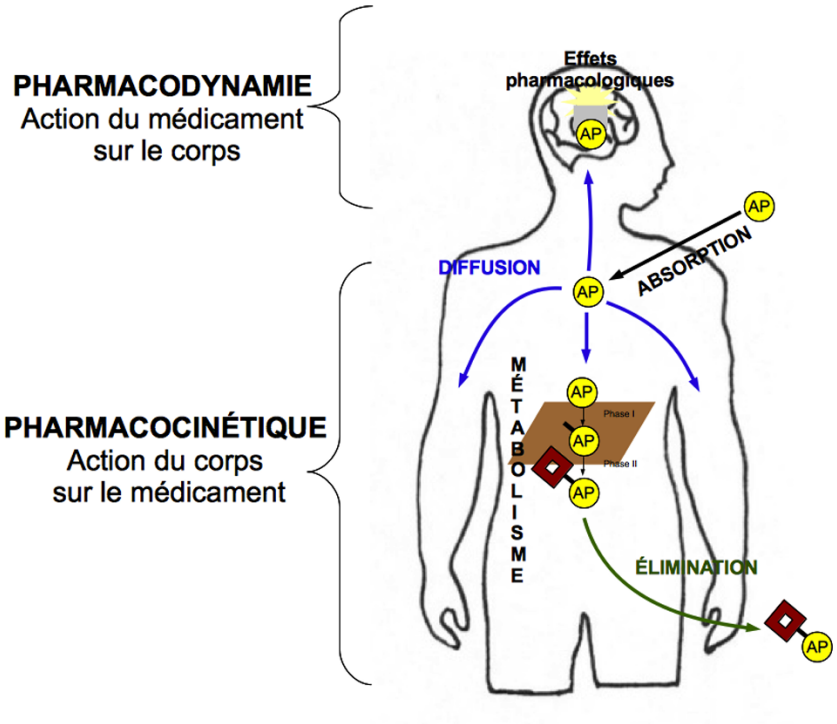
P450. Ce processus est généralement biphasique, avec une phase I qui modifie la molécule originale et une phase II qui la rend plus soluble pour l'excrétion.

4- **Élimination** : L'excrétion du médicament et de ses métabolites, principalement via les reins ou le système biliaire.

La **pharmacodynamie (PD)** se concentre elle sur les réactions entre le médicament et l'organisme, spécifiquement les réponses biologiques à l'introduction de substances exogènes. Elle étudie comment les médicaments interagissent avec leurs sites d'action, souvent des récepteurs moléculaires, et produit des effets mesurables. Les médicaments antipsychotiques, par exemple, interagissent principalement avec les récepteurs D2 et 5-HT2 dans le cerveau(52).
L'intégration des concepts de pharmacocinétique et de pharmacodynamie permet d'anticiper le devenir d'un médicament dans le corps et ses effets thérapeutiques.

Nous présentons ci-dessous un schéma simplifié de la pharmacocinétique et de la pharmacodynamie, et illustré par Lucie Melin.

<u>Schéma représentant le modèle Pharmacocinétique / Pharmacodynamie</u>



B- Les cytochromes P450

Les cytochromes P450 (CYP450) constituent une vaste classe d'enzymes, essentielles dans le métabolisme des composés endogènes et exogènes par biotransformation. Ces enzymes, principalement localisées au sein du réticulum endoplasmique des hépatocytes, facilitent les réactions d'oxydoréduction, convertissant les substances lipophiles en métabolites plus hydrophiles(53). Cela permet leur élimination rénale et prévient l'accumulation de composés potentiellement nocifs(54). La nomenclature des CYP450 dérive de leur capacité caractéristique à absorber la lumière à une longueur d'onde spécifique de 450nm.

La classification des cytochromes P450 s'appuie sur les similitudes de séquence d'acides aminés, regroupées en familles et sous-familles. Un pourcentage d'homologie supérieur à 40% définit une famille (indiquée par un chiffre), tandis qu'une homologie de plus de 55% au sein d'une famille définit une sous-famille (représentée par une lettre). Les isoformes individuelles, ou allèles, sont spécifiées par un chiffre subséquent. Sur les 18 familles de CYP450 identifiées, seulement huit sont responsables de la majorité du métabolisme médicamenteux chez l'homme, incluant CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2E1, CYP2D6 et CYP3A4, en métabolisant 60% de tous les médicaments(55). Parmi les nombreuses isoformes de CYP450, certaines, telles que CYP2D6, CYP3A4, et CYP2C19, sont particulièrement significatives en raison de leur rôle dans le métabolisme d'une grande variété de médicaments, y compris ceux utilisés pour traiter les troubles schizophréniques.

Le CYP2D6 est connu pour métaboliser environ 20% de tous les médicaments prescrits(56), y compris de nombreux antipsychotiques et antidépresseurs. Il présente une diversité génétique considérable entre les individus, ce qui peut conduire à des variations substantielles dans la capacité de métaboliser certains médicaments(57). Par exemple, certaines personnes sont des métaboliseurs lents en raison de certaines variations génétiques, ce qui peut entraîner une accumulation de médicament et un risque accru d'effets secondaires(58). À l'inverse, les métaboliseurs rapides peuvent dégrader les médicaments si rapidement que les concentrations plasmatiques ne sont parfois jamais suffisantes pour être efficaces, menant à un traitement inadéquat.

Le CYP3A4 est une autre isoforme majeure qui métabolise le plus les médicaments utilisés cliniquement(59). Ce cytochrome est particulièrement notable pour sa capacité à métaboliser des médicaments avec une grande variabilité interindividuelle, influencée par des facteurs génétiques, environnementaux, et même certains régimes alimentaires. L'activité de CYP3A4 peut être inhibée ou induite par de nombreux médicaments et substances, ce qui peut conduire à des interactions médicamenteuses complexes, particulièrement problématiques dans le traitement de maladies

telles que les troubles schizophréniques, où les régimes thérapeutiques peuvent inclure de multiples médicaments.

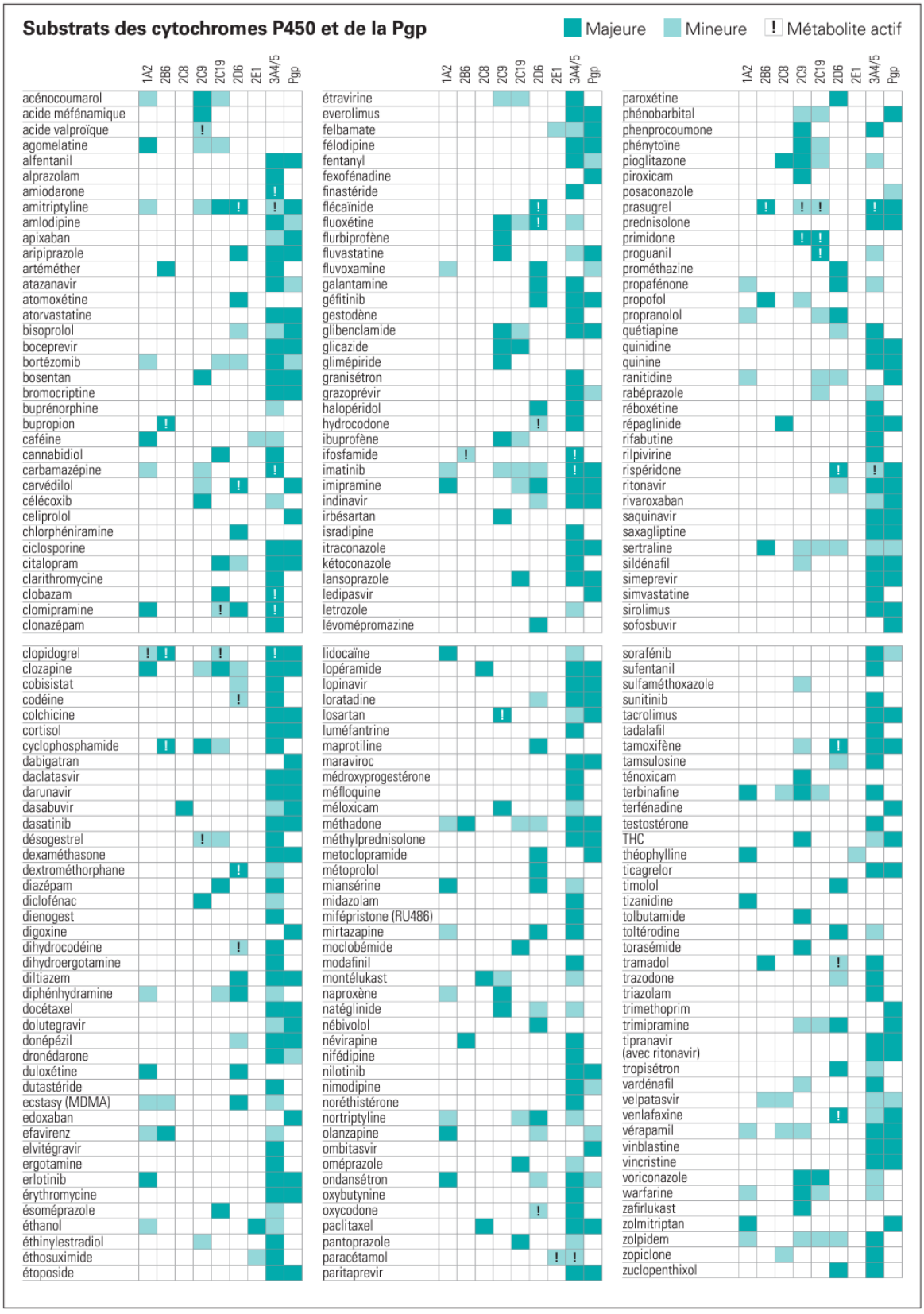
Le CYP2C19 métabolise également un certain nombre de médicaments importants, y compris certains antipsychotiques(60). Comme le CYP2D6, il existe des variantes génétiques qui affectent le fonctionnement de CYP2C19, conduisant à des catégories de métaboliseurs lents et rapides. Cette variabilité peut avoir des conséquences significatives sur l'efficacité et la tolérabilité des médicaments, rendant essentielle une compréhension de l'activité de CYP2C19 pour une pharmacothérapie optimale.

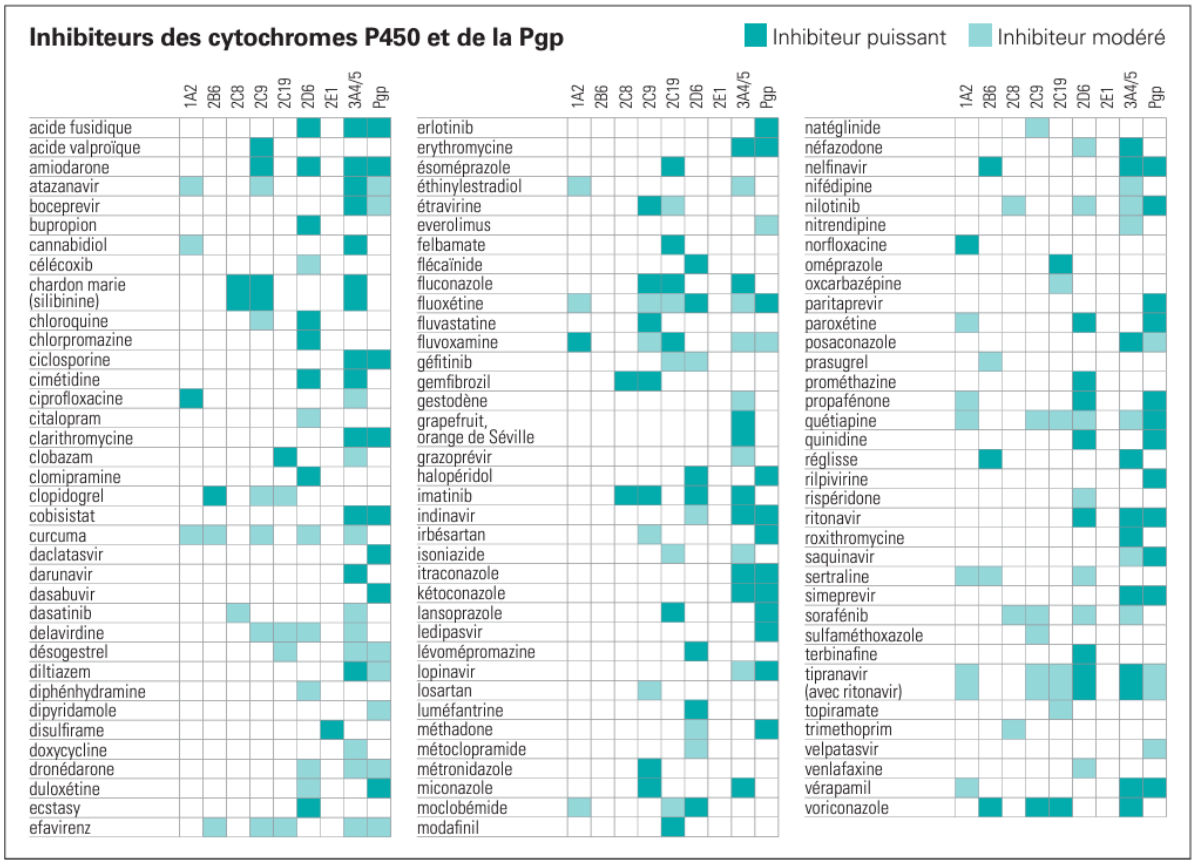
Les CYP450 jouent donc un rôle clé dans la biotransformation des xénobiotiques (comme les médicaments). L'activité métabolique des CYP450 chez les individus peut varier, déterminant des phénotypes métaboliques distincts, allant de métaboliseurs ultrarapides à métaboliseurs lents, influençant ainsi la cinétique et la dynamique des médicaments.

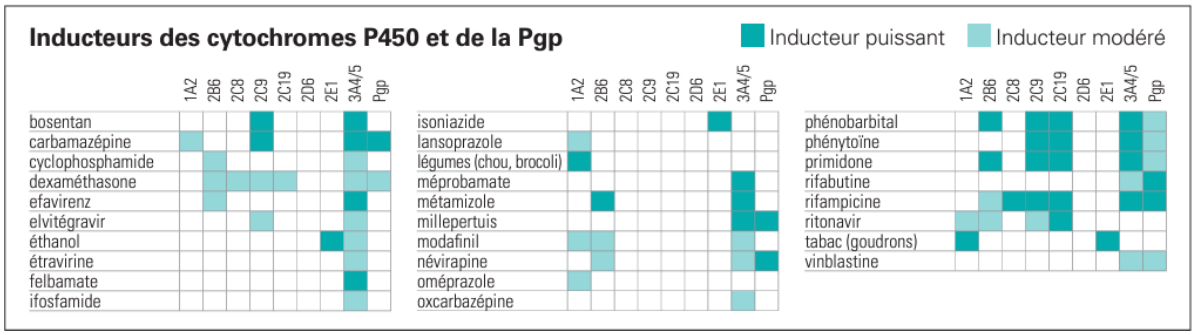
La modulation de l'activité des CYP450 peut se faire par inhibition ou induction(61). L'inhibition par des composés exogènes peut réduire le métabolisme médicamenteux, augmentant le risque d'effets secondaires par accumulation plasmatique du médicament. À l'inverse, l'induction des CYP450, souvent par des médicaments ou des facteurs environnementaux comme le tabagisme(62), peut accélérer le métabolisme, réduisant l'efficacité thérapeutique. Certains médicaments comme les antiviraux, antituberculeux, et certains anticonvulsivants sont connus pour leur capacité à induire les enzymes CYP450. La compréhension de ces interactions est cruciale pour la gestion des thérapies médicamenteuses et la prévention des conséquences cliniques liées à des variations métaboliques individuelles.

Les 2 tableaux ci-dessous proviennent des Hopitaux Universitaires de Genèves. Ils fournissent une liste détaillée des médicaments agissant comme substrats, inhibiteurs, ou inducteurs des différents cytochromes P450 (CYP450) et de la P-glycoprotéine. Il présente des informations spécifiques pour des cytochromes tels que CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, et CYP3A4/5.

Interactions médicamenteuses, cytochromes P450 et P-glycoprotéine (Pgp)







Inhibition

Cytochromes: L'impact dépend de: a) l'importance relative de la voie d'élimination inhibée par rapport à la clairance totale; b) présence ou non de métabolites actifs et c) concentrations d'inhibiteur. A l'arrêt du traitement inhibiteur, l'activité du CYP retourne progressivement à la normale (4 demi-vies). Exemples: l'amiodarone inhibe fortement l'activité du CYP2C9; associée à l'acénocoumarol, substrat du CYP2C9, elle en ralentira l'élimination, d'où un risque d'hémorragie justifiant une adaptation posologique et un suivi INR rapproché. La fluoxétine inhibe fortement l'activité du CYP2D6; associée à la codéine, elle peut en abolir l'efficacité (! signifie que la codéine génère un métabolite actif, la morphine).

P-glycoprotéine: L'impact dépend de l'affinité du substrat pour ce transporteur, de la concentration et de la puissance de l'inhibiteur. Comme pour les CYP, l'activité de la Pgp retourne progressivement à la normale à l'arrêt du traitement inhibiteur (4 demi-vies). Exemple: la ciclosporine inhibe fortement l'activité de la Pgp. Associée à l'indinavir,substrat de la Pgp, elle entraînera une augmentation de sa biodisponibilité.

Induction

Cytochromes: L'impact dépend de: a) importance relative de la voie d'élimination induite par rapport à la clairance totale; b) présence ou non de métabolites actifs et c) concentrations d'inducteur. A l'arrêt du traitement inducteur, l'activité du CYP retourne progressivement à la normale (>2 semaines après disparition de l'inducteur dans le sang). Exemple: Le millepertuis induit progressivement et puissamment l'activité du CYP3A4. Il accélérera fortement l'élimination de l'éthinylestradiol, substrat majeur du CYP3A4, et l'effet contraceptif ne sera plus assuré; il faudra donc prévoir un autre mode de contraception.

P-glycoprotéine: L'impact dépend de l'affinité du substrat pour ce transporteur,de la concentration et la puissance de l'inducteur. Comme pour les CYP, l'activité de la Pgp retourne progressivement à la normale à l'arrêt du traitement inducteur (>2 semaines après disparition de l'inducteur dans le sang). Exemple: la rifampicine induit fortement l'activité de la Pgp. Associée au rivaroxaban, substrat de la Pgp, elle entraînera une diminution de sa biodisponibilité.

C- Pharmacogénétique et premiers épisodes psychotique

Dans le traitement des troubles schizophréniques, l'importance des cytochromes P450 réside dans leur capacité à influencer **l'efficacité et la sécurité des antipsychotiques(63)**. Les variations dans les gènes codant pour ces enzymes peuvent conduire à des différences significatives dans la manière dont les patients métabolisent les médicaments. Cela peut affecter non seulement les niveaux de médicament dans le sang, mais aussi le risque d'effets secondaires et, en fin de compte, l'issue du traitement. Par conséquent, la compréhension de l'activité de CYP450 chez un patient donné peut aider à personnaliser les régimes de traitement, en ajustant les doses et les modalités de prises pour maximiser l'efficacité tout en minimisant les effets secondaires.

L'identification des variations génétiques dans les enzymes CYP450 chez les patients atteints de troubles schizophréniques est donc une étape vers la médecine personnalisée(64). Des tests génétiques peuvent révéler des variations spécifiques qui peuvent prédire la réponse d'un patient à un médicament donné. Cela permet aux médecins de choisir le médicament le plus approprié et de déterminer la dose optimale pour chaque patient, réduisant le risque de réactions indésirables et améliorant les chances de réponse favorable au traitement.

Les cytochromes P450, en particulier CYP2D6, CYP3A4, et CYP2C19, jouent un rôle crucial dans le métabolisme des traitements des troubles schizophréniques. Leur étude et leur compréhension sont essentielles pour la mise en œuvre de stratégies de traitement personnalisées, qui sont de plus en plus reconnues comme un enjeu majeur dans la prise en charge des troubles schizophréniques.

L'application de la pharmacogénétique apparait comme particulièrement intéressante dans les premiers épisodes psychotiques. C'est en effet un **moment crucial pour l'intervention thérapeutique**, et une adaptation personnalisée du traitement peut avoir un impact significatif sur le pronostic à long terme. En comprenant comment les variations génétiques affectent la réponse aux médicaments chez les patients en début de maladie, les psychiatres pourraient comme dans d'autres pathologies médicales (en oncologie notamment) (65) optimiser les schémas thérapeutiques dès le début, améliorant ainsi les chances de réponse favorable et réduisant les risques d'effets secondaires sévères.

Défis et Perspectives :
Bien que prometteuse, l'intégration de la pharmacogénétique dans le traitement des troubles schizophréniques fait face à plusieurs défis. L'un des principaux est la complexité des bases génétiques de la maladie et de la réponse aux médicaments. De plus, les études pharmacogénétiques nécessitent de grands échantillons de population pour valider les associations génétiques. Cependant,

les progrès technologiques en génomique et en bio-informatique offrent des perspectives encourageantes.

La première intervention pharmacologique s'avère importante, car elle peut influencer la trajectoire clinique à long terme du patient(31). La variabilité interindividuelle de la réponse aux antipsychotiques peut significativement affecter l'adhésion au traitement et joue donc sur le pronostic du patient. La pharmacogénétique fournit un cadre pour tenter de comprendre et prédire ces variations, en se concentrant sur les polymorphismes génétiques qui modulent le métabolisme des médicaments antipsychotiques.

Dans ce contexte, j'ai pu présenter ces réflexions en séance plénière à l'université McGill de Montréal, au sein de l'institut du Douglas, et nous avons ensuite publié un article dans la revue *Journal of Psychiatry and Neuroscience* (impact factor 4,3) pour encourager les prescripteurs à utiliser davantage la pharmacogénétique dans la prise en charge des premiers épisodes psychotiques.

The information in this column is not intended as a definitive treatment strategy but as a suggested approach for clinicians treating patients with similar histories. Individual cases may vary and should be evaluated carefully before treatment is provided. The patient described in this column is a composite with characteristics of several real patients.

Utilizing pharmacogenetics when treating first episode psychosis

Theo Korchia, MD; Ridha Joober, MD, PhD; Raphaelle Richieri, MD, PhD; Priyadharshini Sabesan, MD; Lena Palaniyappan, MD, PhD

The parents of a 21-year-old man brought him to an emergency psychiatric clinic for disturbed behaviour. He displayed significant hallucinatory behaviour, prominent delusions of persecution involving "special forces" and notable disorganization of speech, and had experienced more than 8 months of socio-occupational dysfunction. Upon admission, neurologic examination was unremarkable and results of routine metabolic, endocrine, liver and renal screening were within normal limits. He met the diagnostic criteria for schizophrenia, with a first episode of untreated psychosis.

He was prescribed 10 mg aripiprazole for 4 days, but quickly developed adverse effects with disabling extrapyramidal rigidity. He then was switched to 2 mg risperidone, but after 1 week, he presented hypersalivation and debilitating daytime sleepiness. Despite ongoing hallucinations and persecutory fears, he refused the options of clozapine, olanzapine and quetiapine owing to concerns about weight gain, but he accepted haloperidol. He was put on 5 mg haloperidol, but he soon reported tremors, stiffness and a notable anhedonia.

At this stage, we sought a cytochrome P450 (*CYP450*) genotype assay for *2C19* and *2D6*. The patient was found to be a normal (extensive) metaboliser for *2C19* but a poor metaboliser (PM) for *CYP2D6*.

Haloperidol, aripiprazole and risperidone are likely to be degraded too slowly in patients who are *CYP2D6* PM, leading to treatment failure, and risperidone is likely to be too slowly converted to its active metabolite, leading to a greater risk of adverse effects. The patient consented to be switched to paliperidone, and a rapid antipsychotic response followed over the next 10 days. The patient was discharged on 6 mg/d paliperidone and had a score of 2 on the Clinical Global Impressions Scale of Severity at 6 months.

Most antipsychotics are hepatically metabolized by several CYP450 enzymes, but some, like paliperidone or amisulpride, are less metabolized than others.[1] In clinical practice, pharmacogenomic testing of *CYP2D6* and *CYP2C19* is seldom done, likely because many prescribers do not consider genetic factors to be critical for treatment choice, dose titration or adverse effect reduction.[2] The prevalence of PMs and ultra-rapid metabolizers (UM) is estimated to be less than 5% in Europeans (with notable variations across other ethnicities[4,5]); preventive testing is deemed to have low yield in practice. Thus, the maximum daily doses recommended for antipsychotics are based on a genotype-weighted population equilibrium that ignores the clinical relevance of *CYP2C19*/*CYP2D6* metabolizer categories. Nevertheless, several product labels offer dosing recommendations based on metabolizer status,[2] and many commercial tests are now available to assist prescribers.[5]

Of relevance to the present case is a recent large retrospective observational study confirming the higher frequency of treatment failures in PMs.[6] *CYP2D6* PMs are 2–3 times more frequent than UMs among Europeans,[3] with a notable dose reduction for aripiprazole and risperidone often reported in PMs.[6,7]

In patients with a first episode of psychosis, where a good response to pharmacotherapy is expected in most cases, the presence of repeated treatment failures and/or higher sensitivity to adverse effects should incite clinicians to order pharmacogenetic testing. This is particularly true if there are no other factors that explain poor response (e.g., noncompliance, drug abuse) or high sensitivity to adverse effects (e.g., medications interfering with the CYP system, a phenomenon known as "phenoconversion").[8]

In clinical practice, pharmacogenetic variations may not explain all of the variance in drug metabolism, and it is important that we consider sex,[9] age, concomitant medications, renal/hepatic status, lifestyle factors such as smoking, and weight when making antipsychotic prescribing decisions. Further, dosing and monitoring drug concentration may be more readily available and directly inform dose adjustments, complementing pharmacogenetic testing. Nevertheless, studies of real-world utility of pharmacogenetic testing indicate that certain subgroups, such as the most severely ill[10] or those who are nonadherent to treatment,[11] may have substantially greater odds of improvement when prescribing follows pharmacogenetics-based recommendations. Regarding antipsychotics, prescribing guidelines have been developed only for CYP2D6[2] and CYP3A4,[12] and the evidence for testing other variants[13] has not yet been deemed sufficient to make more general recommendations.

Increasing prescribers' use of pharmacogenetic testing in psychosis programs, especially when facing inadequate treatment response, has the potential to improve remission rates and reduce overall adverse effects associated with antipsychotics in clinical practice.

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D- Le risque suicidaire en fonction du métabolisme

Le suicide représente une urgence clinique prééminente dans la prise en charge des psychoses débutantes(66), constituant l'une des principales causes de mortalité chez ces patients. Cela peut notamment être en lien direct avec la symptomatologie hallucinatoire (syndrome d'influence) incitant le patient à se faire du mal, ou plus fréquemment avec le vécu complexe d'une telle maladie. Les symptomes négatifs peuvent alors être primaires ou secondaires, à la suite du syndrome positif(67). La période suivant l'apparition d'une psychose est en effet marquée par une vulnérabilité accrue, où les symptômes psychotiques intensifiés peuvent conduire à un désespoir profond, à une détresse psychologique et à une perturbation marquée du jugement et de l'insight(68), augmentant substantiellement le risque de comportements suicidaires(69). La surveillance et l'intervention précoces sont donc impératives pour atténuer ce risque.

Nous avons publié une méta-analyse dans *Schizophrenia Bulletin* (70) qui révélait que l'épisode dépressif caractérisé sévère était fréquemment comorbide chez les patients souffrant de troubles schizophréniques, avec une prévalence estimée à 32,6%. L'étude avait identifié plusieurs facteurs influençant cette prévalence, tels que l'âge, le niveau d'éducation et l'utilisation d'antidépresseurs. Cette forte prévalence soulignait le besoin d'une reconnaissance et d'une prise en charge accrues de la dépression chez les patients souffrant de troubles schizophréniques par les professionnels de santé, pour limiter le risque suicidaire.

Les facteurs contribuant à l'augmentation du risque de suicide chez les patients souffrant de premiers épisodes psychotiques sont multiples et comprennent des symptômes dépressifs concomitants, une anxiété significative, ainsi que des pensées et des comportements de persécution qui peuvent être exacerbés par les hallucinations et les délires(68). La stigmatisation associée à la maladie mentale et la désorganisation sociale et professionnelle qui en résulte renforcent également le sentiment d'isolement et de désespoir, conduisant à une considération suicidaire comme issue à la souffrance psychique(71).

Il est donc capital de se pencher sur les stratégies de prévention du suicide dès les premiers stades des troubles psychotiques. Une évaluation rigoureuse du risque suicidaire, impliquant une anamnèse détaillée et une évaluation continue des idéations et comportements suicidaires, doit être intégrée dans le plan de traitement. Cette évaluation est d'autant plus essentielle lors de l'initiation ou des changements de régime antipsychotique, périodes pendant lesquelles les patients peuvent être particulièrement instables.

L'attention portée à la **pharmacogénétique** peut jouer un rôle dans la **prévention du suicide** en personnalisant le traitement antipsychotique pour réduire la charge des effets secondaires et optimiser l'efficacité, contribuant

ainsi à une meilleure adhésion au traitement et à une réduction des symptômes psychotiques qui sont souvent en corrélation avec les risques suicidaires. La sélection d'antipsychotiques en fonction du profil génétique métabolique peut permettre d'éviter les concentrations plasmatiques toxiques ou sub-thérapeutiques, qui peuvent exacerber la détresse psychologique ou l'inefficacité du traitement, deux facteurs fortement associés au risque suicidaire.

Dans ce contexte et dans cette population jeune, le suivi étroit de la réponse au traitement et l'ajustement des stratégies thérapeutiques sont essentiels(72). L'intégration d'interventions psychosociales et de soutien psychothérapeutique, en tandem avec la pharmacothérapie, peut fournir un réseau de sécurité supplémentaire, atténuant la détresse et renforçant les mécanismes d'adaptation du patient. Enfin, impliquer la famille (73)et le réseau de soutien social du patient dans le plan de soins peut aider à surveiller les signes avant-coureurs de comportement suicidaire et à fournir une intervention rapide et efficace(74).

L'article original que nous avons soumis pour publication constitue une avancée significative dans la compréhension des mécanismes qui sous-tendent la variabilité des réponses aux traitements antipsychotiques et aux antidépresseurs. Cette recherche s'inscrit dans une démarche innovante et nécessaire pour répondre à un enjeu majeur en psychiatrie : la réduction des comportements suicidaires chez les patients atteints de troubles schizophréniques, indépendamment de leur âge.

Notre étude met en lumière l'association entre les phénotypes métaboliseurs ultrarapides (UM) pour les enzymes CYP2C19 et CYP2D6 et un risque accru de tentatives de suicide. L'identification précoce des patients UM pourrait ainsi permettre d'ajuster les protocoles thérapeutiques de manière à atteindre des concentrations plasmatiques optimales des médicaments, cruciales pour la réponse clinique et la prévention du suicide.

À travers ce travail original, nous montrons que la prise en compte des particularités métaboliques individuelles est non seulement envisageable mais surtout, qu'elle est porteuse d'espoir pour améliorer significativement les stratégies de prise en charge en matière de prévention du risque suicidaire.
Notre étude souligne donc l'urgence et la nécessité d'intégrer les données pharmacogénétiques dans les pratiques cliniques quotidiennes, pour offrir aux patients une médecine de précision, plus sûre et plus efficace.

L'Encéphale

UM CYP450 metabolizers are at higher risk of suicide attempts in schizophrenia

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CYP2D6 and CYP2C19 ultrarapid metabolism is associated with suicide attempts in schizophrenia.

Le métabolisme ultrarapide des CYP2D6 et CYP2C19 est associé aux tentatives de suicide dans la schizophrénie.

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Abstract (233 words)

Introduction: Genetics polymorphisms in genes encoding enzymes metabolizing psychotropics drugs result in various isoenzymes with different catalytic efficacy. Of particular interest, some of these isoenzymes are highly catalytic leading to an Ultra-rapid metabolism (UM) of their substrate medication, which in turn results in lower medication concentrations and possibly poor clinical outcomes, including a higher risk for suicidal behaviour. In this study, we investigate the role of CYP2C19 (metabolizing most antidepressant medications) and CYP2D6 (important in metabolizing antipsychotics) UM isoenzymes on suicidal behavior among a cohort of patients with schizophrenia.

Methods: 178 patients diagnosed with schizophrenia were recruited from the day hospital of a regional psychiatric academic hospital. We compared lifetime suicide attempts between groups of patients stratified according to their enzymatic profile. Several socio-demographics and clinical covariants were controlled for.

Results: Among the 178 patients, 16 and 44 were UM as determined by their CYP2D6 and CYP2C19 genotype respectively. Univariate analysis showed a significant association between suicidal attempts and CYP2D6 and CYP2C19 UM status (p =0.041 and p=0.029 respectively). These associations remained significant in multivariate analyses (adjusted for age, sex, dose exposure and antidepressant use) for both CYP2D6 (p = 0.020, OR = 4,096, 95% CI [1.25-13.48]) and CYP2C19 (p = 0.016, OR =2.680, 95% CI [1.21-5.95]).

Conclusion: This study suggests that the UM phenotypes for both CYP2D6 or CYP2C19 are associated with an increased risk for suicide attempts in patients with schizophrenia.

Keywords: antipsychotic, psychosis, metabolism, suicide, self-harm

Résumé (233 mots)

Introduction : Les polymorphismes génétiques dans les gènes codant pour les enzymes métabolisant les médicaments psychotropes donnent naissance à diverses isoenzymes dont l'efficacité catalytique varie. Il est particulièrement intéressant de noter que certaines de ces isoenzymes ont une efficacité catalytique élevée, ce qui entraîne un métabolisme ultra-rapide (UM) de leur substrat médicamenteux, qui se traduit à son tour par des concentrations médicamenteuses plus faibles et éventuellement par de mauvais résultats cliniques, y compris un risque plus élevé de comportement suicidaire. Dans cette étude, nous étudions le rôle des isoenzymes CYP2C19 (qui métabolisent la plupart des antidépresseurs) et CYP2D6 (important dans le métabolisme des antipsychotiques) sur le comportement suicidaire d'une cohorte de patients atteints de schizophrénie.

Méthodes : 178 patients diagnostiqués avec une schizophrénie ont été recrutés dans l'hôpital de jour d'un hôpital universitaire psychiatrique régional. Nous avons comparé les tentatives de suicide au cours de la vie entre des groupes de patients stratifiés en fonction de leur profil enzymatique. Plusieurs facteurs sociodémographiques et covariants cliniques ont été pris en compte.

Résultats : Parmi les 178 patients, 16 et 44 étaient UM selon leur génotype CYP2D6 et CYP2C19 respectivement. L'analyse univariée a montré une association significative entre les tentatives de suicide et les statuts CYP2D6 et CYP2C19 UM (p =0,041 et p=0,029 respectivement). Ces associations sont restées significatives dans les analyses multivariées (ajustées sur l'âge, le sexe, la dose d'exposition et l'utilisation d'antidépresseurs) à la fois pour le CYP2D6 (p = 0,020, OR = 4,096, 95% CI [1,25-13,48]) et le CYP2C19 (p = 0,016, OR = 2,680, 95% CI [1,21-5,95]).

Conclusion : Cette étude suggère que les phénotypes UM pour CYP2D6 ou CYP2C19 sont associés à un risque accru de tentatives de suicide chez les patients atteints de schizophrénie.

Mots clés : antipsychotique, psychose, métabolisme, suicide, automutilation

1. Introduction

Schizophrenia (SZ) is arguably the most disabling mental disorder, and is ranked among the 10 most disabling conditions according to the World Health Organization(1). It affects roughly 21 million people worldwide (2). Patients with SZ have shorter life expectancies compared to the general population (3). It is estimated that up to 40% of this excess of premature mortality is attributed to unnatural deaths (4), including suicide, an outcome that afflicts 6% of patients with schizophrenia (5).
The first line treatement for schizophrenia is based on antipsychotic medications that are highly effective in controlling positive symptoms. However therapeutic response is highly variable between patients. This variability could be attributed to many factors, including variability in drug inactivation (6,7). Antipsychotics are mainly inactivated through the cytochromes P450 (CYP) system, a complex system with various isoenzymes, each having a specific catalytic activity. These isoenzymes are encoded by a number of genetic variants. These polymorphisms result in various enzymatic profiles grouped into four phenotypes: poor (PM), intermediate (IM), normal (NM) or ultrarapid (UM) metabolizers, which are correlated with variations in plasma concentrations of substrate drugs.

In this study, our main hypothesis is that patients with a UM phenotype, who have overall lower medication concentration compared to the three other phenotypes, may be chronically sub-optimally treated and may suffer poorer outcomes including higher rates of suicidal behaviour. This is particularly plausible as metabolic profiles are not determined and drug doses are not adjusted accordingly in usual clinical practice.
Here, we focused on two enzymatic profiles which are particularly interesting form a psychiatric pharmacotherapy standpoint: CYP2D6 and CYP2C19 UM. CYP2C19 metabolizes most antidepressant medications, while CYP2D6 is particularly important in the metabolism of antipsychotics. We focused on these two cytochromes based on the hypothesis that differences in the metabolism of psychotropics could lead to higher frequency for treatment changes and/or adverse effects (8,9).
In previous genetic studies, the CYP2C19 UM has been associated with suicidality in patients with major depressive disorder (MDD) although with some inconsistencies (10,11)The role of CYP2D6 in suicidal behavior polymorphisms has also been suggested (12–14). Second, CYP2D6 is involved in the metabolism of many antipsychotic and antidepressant drugs (15).
Altogether, the CYP2C19 and 2D6 polymorphisms could influence not only the variability in drug response, but also disease susceptibility in patients suffering from SZ, as well as comorbidities like depression and suicide risk.
In a prospective and naturalistic study, we investigated the impact of CYP2C19 and 2D6 UM on suicide behaviors in SZ.

2. Methods

2.1 Study participants

178 patients were consecutively recruited in the psychiatric academic day hospital from Sainte-Marguerite hospital, Marseille, France, from May 2011 to December 2016. The inclusion criteria were: (1) age ≥ 18 years, (2) diagnosis of SZ according to the DSM-IV-TR criteria, (3) French as native language (4) clinically stable with ongoing treatment (for at least 8 weeks). The exclusion criteria were as follows: (1) diagnoses other than SZ on axis 1 of the DSM-IV-TR, except for nicotine dependence, (2)major general medical conditions that explain psychiatric symptoms, (3) mental retardation or organic mental disorders.

All the patients were informed of the study and gave written informed consent. The study was designed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Aix-Marseille University as well as by the *Commission Nationale de l'Informatique et des Libertés* (CNIL number 1223715).

2.2 Data collection

Socio-demographic and clinical characteristics: duration of illness and age at illness onset, body mass index (BMI), tobacco use, psychotic symptoms based on the Positive and Negative Syndrome Scale (PANSS) five factors (negative, positive, excited, depressive, cognitive) (16,17) and depressive symptoms based on The Calgary Depression rating Scale for Schizophrenia (CDSS) (18,19), Fagerström Test for Nicotine Dependence (20), Global Assessment Functioning (GAF) (21), Clinical Global Impression scale (CGI) (22) and the Medical Adherence Rating Scale (MARS) (23). Depression diagnosis was determined by the CDSS score: a score above 6 has been associated with the presence of major depressive disorder (24). The sensibility and the specificity of the CDSS to diagnose depression in patients with schizophrenia is considered as satisfactory (18,19). In this study, depression diagnosis was determined by the CDSS total score (score ≥ 6).

1. Drug information: antipsychotic medications and chlorpromazine equivalent doses (in milligrams per day), antidepressant medications.
2. Lifetime history of suicide attempts: evaluated during the medical interview. All suicide attempts that led to a visit to the emergency room or to medical care were listed in the patient's medical file. A history of attempted suicide was also questioned during the medical interviews. Finally, and with the patients' agreement, the families of the patients could be solicited for information related to suicidal behaviors. In each case, the medical file was fully scrutinized by 3 clinicians to ensure no recorded attempts are missed.
3. Genotyping of CYP2D6 and CYP2C19: The molecular biology laboratory (*CHU Conception*) centralized and processed data to determine the CYP2D6 genotype from blood samples of patients. Genomic DNA was prepared using QIAsymphony device (Qiagen). Single nucleotide

polymorphisms (SNPs) of exon 1-6 and intron 6-7 of CYP2D6 gene were genotyped by sequencing PCR products using a 3500 Xl Dx device (Applied Biosystems, Foster City, California) as described by Ann K. Daly (25). The TaqMan® analysis system (Applied Biosystems, Foster City, California) was used to detect duplications of the CYP2D6 gene and its CYP2D6*5 deletion. SNPs corresponding to the CYP2C19*2 and CYP2C19*17 alleles (NCBI SNP ID: rs4244285 (681G> A) and rs12248560 (-806C> T)) were genotyped by sequencing the products of PCR from 5′-UTR and exon 5. Direct sequencing was performed by the same device as for CYP2D6. The studies of Blaisdell and Fukushima-Uesaka made it possible to carry out these amplification and sequencing of the PCR thanks to the primers(26,27).

2.3 Nomenclature, allele allocation and activity score

The allelic nomenclature has been assigned to the CYP450 haplotypes to ensure standardization in the denomination of different genetic polymorphisms (28). The diplotype allows to categorize CYP450 into functional groups, based on the predicted activity of the encoded enzyme (29). Caudle et al. have developed a scoring system that provides a consistent approach to the predicted phenotype (30), which is approved and recommended by the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the *Dutch Pharmacogenetics Working Group* (DPWG). This CYP2D6 activity score was obtained by summing the sub-score assigned to each diplotype. The predicted phenotype, based on this activity score, was assigned as follows: UM for a score greater than 2.25; NM for a score between 1.25 and 2.25; IM for a score between 0.25 and 1, and PM for a score of 0.

The CYP2C19 predicted phenotype was: i) NM for a patient carrying two functional alleles; ii) IM for a patient carrying either one functional allele associated with CYP2C19*2 allele, or CYP2C19*17 allele associated with CYP2C19*2 allele; iii) PM for a patient carrying CYP2C19*2 diplotype and iv) UM for a patient carrying either CYP2C19*17 diplotype.

Extreme metabolizers were defined by a predicted UM or PM phenotype for CYP2D6 and CYP2C19.

2.4 Statistical Analyzes

Statistical analyzes compared the following groups: patients suffering from schizophrenia with presence of suicide attempt, and patients suffering from schizophrenia with absence of suicide attempt. Socio-demographics and clinical characteristics were presented using measures of mean and standard deviation for continuous data and frequency distribution for categorical variables. Univariate analyses were performed using the chi-square test for categorical variables and the Student t-test for continuous variables.

To explore the relationships with CYP2D6 UM and CYP2C19 UM on the one hand and clinical characteristics in schizophrenia on the other, we used a multivariate linear regression model for

continuous variables and a logistic regression model for categorical variables. Variables with p values < 0.20 in univariate analysis were included in the multivariate analysis (substance use disorder, chlorpromazine equivalent, presence of antidepressants, CYP450 status). Gender and age were forced. The final models included β and 95% confidence intervals. All tests were two-sided, with an α level set at 0.05. Statistical analyses were performed using the SPSS software version 20 package (SPSS Inc., Chicago, IL, USA).

3. Results

3.1 Patient characteristics

We included 178 patients suffering from SZ. Among them, the prevalence of the different UM metabolizers was 9% (n=16) and 24.7% (n=44) for the CYP2D6 and the CYP2C19 respectively (Table 1).

The mean age of the patients was 35.01 years (± 11.5) and 71% (n=126) were males. They had moderately severe symptoms with a mean PANSS total score of 73.55 (±21.12). The mean chlorpromazine equivalent dose was 909.9 mg (± 853.1) and 62.4% (n=111) were substance (tobacco, cannabis, alcohol) users. The mean duration of illness was 13.1 (± 9.7) years.

3.2 Univariate analysis.

There was no significant difference between the 2 groups (presence or absence of lifetime suicide attempt) with respect to gender, age, education level, employment status, duration of disorder, BMI, metabolic syndrome or CRP level.

In contrast, we found a strong statistical relationship between the presence of suicide and lifetime substance misuse ($p = 0.019$), current use of antidepressants ($p = 0.007$) and CYP450 status: CYP2D6 UM ($p = 0.041$) and CYP2C19 UM ($p = 0.029$).

3.3 Multivariate analysis.

In order to explore the relationship between CYP450 UM patients and presence of suicide attempt, we performed multivariate linear and logistic regressions analyses by adjusting for sex, age, chlorpromazine equivalent doses, duration of illness, and presence of antidepressants.

Association between CYP2D6 UM and higher presence of suicide attempts remains significant ($p = 0.020$, OR = 4.096, CI [1.25-13.48]) likewise association between CYP2C19 UM and suicidal behaviour remained significant ($p = 0.016$, OR =2.680, 95% CI [1.21-5.95]).

We also found a significant relationship between lifetime substance misuse of tobacco, cannabis, alcohol ($p = 0.026$, OR = 2.565, 95% CI [1.12-5.89]) and presence of suicide attempts.

4. Discussion

This study investigated the relationship between the CYP450 polymorphisms and suicide attempts, in a population of 178 French outpatients suffering from SZ.

We found that patients suffering from SZ with a CYP2D6 UM type are at increased risk for lifetime suicide attempt (OR = 4.096). This was also the case for patients with CYP2C19 UM (OR = 2.680). Sex, age, current depressive symptoms, and treatments did not influence this relationship. Thus, UM status for CYP2D6 or CYP2C19 in SZ could be considered as a risk factor for increased lifetime suicide behaviour.

The international society of Psychiatric Genetics showed that allelic variation in the genes encoding the CYP2D6 and CYP2C19 lead to differences in the metabolism of numerous medications relevant in psychiatry, in particular antidepressants and antipsychotics. Thus, patients with extreme metabolism phenotypes are especially at increased risk for adverse events, and some evidence suggests that such patients are less likely to respond to treatment (6,31). Indeed, most clinically relevant genetic variations are connected to genetic polymorphism of CYP2C19 and CYP2D6 (32).

In general, the link between suicidality and CYP450 UM is more often put forward with CYP2C19 since it metabolizes antidepressant treatments, and that it may be responsible for an ineffective rate of antidepressants, sometimes resulting in suicide attempts. Indeed, CYP2C19 is involved in the metabolism of many antidepressants, especially for sertraline, escitalopram and citalopram (33) and CYP2D6 metabolizes most prescribed psychotropic drugs (34).

In a recent study that retrospectively investigated suicide in depressed patients treated with citalopram (metabolized by CYP2C19 and CYP2D6), there were more patients with extreme metabolizer (PM and UM) phenotypes for CYP2C19 among patients who died by suicide (35), but this difference was not found for extreme metabolizers for CYP2D6. A previous study showed that high CYP2C19 enzymatic activity was associated with higher suicidality in depressed suicide attempters(10).

Similarly, some authors showed that, among patients suffering from MDD and medicated with escitalopram, CYP2C19 UM metabolism was related to lower serum escitalopram levels that could explain the antidepressant failure (36,37).

Nevertheless, the link between suicide attempt and CYP2D6 polymorphisms is far from being a conclusive one. Peñas-Lledo et al. found an association between CYP2D6 and suicide risk in eating disorders (Peñas-Lledó et al. 2011), and in a population suffering from different mental disorders, but the authors did not include SZ disorders (Peñas-Lledó et al. 2015). In a large psychiatric population with a lifetime history of suicide attempts, the same authors found among the "severe" suicide attempt population, a higher amount CYP2D6 UM compared to the rest of the sample (Peñas-Lledó et al. 2012). In the same way, among patients who died by suicide, there was a higher number of patients carrying more than two active CYP2D6 genes (corresponding to the UM phenotype) compared to those who died by natural causes (natural-death cases)(14). Furthermore, this association has been replicated in unipolar and bipolar depression (40).

However, some studies did not find association between CYP2D6 phenotypes and suicide attempts in MDD (11) and in SZ (12). Moreover, another study with a large sample of psychiatric in-patients did not find any difference in the rate of suicide attempts between CYP2D6 UM and non-UM participants, although, the authors assumed that CYP2D6 UM status might be associated with increased risk of suicidality within restricted subpopulations (41). However, this study included only 4 patients with CYP2D6 UM and a diagnosis of SZ, which questions the statistical power of this study.

While the the relationship between CYP enzymes and suicidal behaviour is best framed within a pharmaco- kinetic hypothesis of psychotropics, different cytochromes P450 like CYP2D6, CYP2C19, CYP3A4 or CYP1A2 isoenzymes are expressed in the fetal brain and may affect metabolism of monoaminergic neurotransmitters, neurodevelopment and may contribute to the pathophysiology of mental disorders (42), including suicidal behaviour. Furhermore, CYP2D6 and CYP2C19 also metabolize critical endogenous substrates relevant for affect regulation (43,44); polymorphic variations could thus directly affect comorbidities and suicidal risk in schizophrenia.

In addition, association studies between the CYP2D6 polymorphism and SZ have been reported although with some inconsistencies. Indeed, some authors have shown an under-representation of PM in SZ patients (45,46), or an over-representation of CYP2D6 UM in this disorder (47); while other studies were unable to identify any association (48).

Some limitations should be considered when interpreting the results of this study. First, even if we included a relatively large sample of patients with SZ the number of CYP2D6 or CYP2C19 UM metabolizers remains relatively small. Further studies are needed to replicate these results in larger populations. Second, as the variability of the prevalence of each metabolism is related to ethnic origins, further studies should take into account the ethnicity of recruited patients (15,49,50).

5. Conclusion

Our results suggest that patients suffering from SZ and presenting a CYP2D6 UM or CYP2C19 UM metabolism have an increased risk of suicide attempts, which could be reduced being aware of metabolic status and adapting psychotropic treatments. Particular attention should also be paid to reducing toxic substances in this population, which is already at high risk of attempted suicide. As the cost of genetic testing continues to decrease, genotyping of CYP2D6 and CYP2C19 may become a routine test before prescribing relevant antidepressants to all patients (51). Further studies are needed to understand mechanisms of CYP2D6 activity in the brain and whether the observed relationship is mediated by the role of CYP2D6 involvement in drug metabolism and/or other processes relevant to the pathogenisis of schizophrenia.

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				Univariate analysis			Multivariate analysis
	Entire Group N=178	Absence of suicide attempt (lifetime) N=128 (71.9%)	Presence of suicide attempt (lifetime) N=50 (28.1%)	*p value*	OR	[CI95%]	*Adjusted p value*
Socio-demographic characteristics							
Sex, n (%)							
Men	126 (70.8%)	92 (71.9%)	34 (68.0%)				
Women	52 (29.2%)	36 (28.1%)	16 (32.0%)	0.609	1.588	0.707-3.567	0.263
Age (years), mean (SD)	35.01 (11.54)	35.40 (11.74)	34.02 (11.08)	0.474	0.980	0.948-1.013	0.240
Education level (>12 years), n (%)	98 (55.1%)	71 (55.5%)	27 (54.0%)	0.859			
Working force status, n (%)	14 (7.9%)	8 (6.2%)	6 (12.0%)	0.200			
Duration of disorder (years), mean (SD)	13.01 (9.70)	13.13 (9.73)	12.70 (9.72)	0.794			
Clinical characteristics							
First generation antipsychotics, n (%)	34 (19.1%)	24 (18.8%)	10 (20.0%)	0.849			
Chlorpromazine equivalent, mean (SD)	909.95 (853.14)	836.51 (790.45)	1096.50 (978.86)	0.068	1.000	1.000-1.001	0.079
Clozapine, n (%)	47 (26.4%)	30 (23.4%)	17 (34.0%)	0.151	1.473	0.660-3.285	0.344

		Univariate analysis			Multivariate analysis		
	Entire Group N=178	Absence of suicide attempt (lifetime) N=128 (71.9%)	Presence of suicide attempt (lifetime) N=50 (28.1%)	*p value*	OR	[CI95%]	*Adjusted p value*
Antipsychotics polytherapy	169 (94.9%)	120 (93.8%)	49 (98.0%)	0.448			
At least one CYP2D6 substrate, n (%)	104 (58.4%)	73 (57.0%)	31 (62.0%)	0.545			
At least one CYP2C19 substrate, n (%)	16 (9.0%)	9 (7.0%)	7 (14.0%)	0.144	0.609	0.139-2.667	0.510
All inhib 2D6, n (%)	38 (21.3%)	22 (17.2%)	16 (32.0%)	**0.030**	0.921	0.215-3.940	0.911
All inhib 2C19, n (%)	8 (4.5%)	4 (3.1%)	4 (8.0%)	0.223			
Antidepressants (presence), n (%)	52 (29.2%)	30 (23.4%)	22 (44.0%)	**0.007**	2.813	0.833-9.505	0.096
Benzodiazepines (presence), n (%)	63 (35.4%)	47 (36.7%)	16 (32.0%)	0.554			
Current symptomatology							
PANSS total score, mean (SD)	73.55 (21.12)	73.85 (21.52)	72.78 (20.31)	0.762			
CDSS total score, mean (SD)	3.93 (4.27)	3.62 (4.04)	4.72 (4.76)	0.140			
MARS, mean (SD)	6.66 (2.12)	6.70 (2.03)	6.56 (2.35)	0.706			
Substance use disorder							
Lifetime substance misuse (tobacco, cannabis, alcohol), n (%)	111 (62.4%)	73 (57.0%)	38 (76.0%)	**0.019**	2.565	1.117-5.892	**0.026**

		Univariate analysis					Multivariate analysis
	Entire Group N=178	Absence of suicide attempt (lifetime) N=128 (71.9%)	Presence of suicide attempt (lifetime) N=50 (28.1%)	*p value*	OR	[CI95%]	*Adjusted p value*
CYP450 status							
CYP2D6 UM, n (%)	16 (9.0%)	8 (6.2%)	8 (16.0%)	**0.041**	4.096	1.245-13.475	**0.020**
CYP2C19 UM, n (%)	44 (24.7%)	26 (20.3%)	18 (36.0%)	**0.029**	2.680	1.206-5.954	**0.016**
Biological characteristics							
BMI, mean (SD)	26.50 (5.16)	26.43 (4.89)	26.70 (5.86)	0.759			
Metabolic Syndrome, n (%)	26 (14.6%)	16 (12.5%)	10 (20.0%)	0.203			
High CRP level, n (%)	68 (38.9%)	48 (38.4%)	20 (40.0%)	0.844			

E- Pharmacogénétique et clozapine dans les premiers épisodes psychotiques

La clozapine est un antipsychotique atypique unique, reconnu pour son efficacité supérieure dans la prise en charge des troubles schizophréniques résistants au traitement(75). Depuis son introduction dans les années 1970, la clozapine a transformé l'approche thérapeutique des cas les plus résistants de troubles schizophréniques, là où les antipsychotiques classiques échouent à atténuer les symptômes(76).

Son mécanisme d'action se distingue par une affinité relativement faible pour les récepteurs dopaminergiques D2 et une plus grande affinité pour les récepteurs sérotoninergiques 5-HT2A, ce qui peut contribuer à son profil d'efficacité unique, notamment dans la réduction des symptômes positifs, négatifs et cognitifs des troubles schizophréniques(77). Les études montrent que la clozapine est particulièrement efficace pour réduire les risques de réhospitalisation (78) et améliorer la qualité de vie des patients (79). De plus, elle a été associée à une **réduction des comportements suicidaires** chez les patients souffrant de troubles schizophréniques, une découverte d'une importance capitale étant donné la prévalence élevée de la suicidabilité dans cette population (80).

Cependant, la clozapine est connue pour sa marge thérapeutique étroite et sa variabilité pharmacocinétique interindividuelle. Cela signifie que les concentrations plasmatiques efficaces et sécuritaires de la clozapine peuvent varier considérablement d'un individu à l'autre, rendant essentiel le suivi thérapeutique pharmacologique (STP) pour optimiser les doses individuelles(81). Le STP permet d'ajuster précisément la dose pour maintenir les niveaux plasmatiques dans une gamme thérapeutique optimale, minimisant ainsi les effets secondaires potentiellement graves tels que la neutropénie ou la cardiomyopathie.

En ce qui concerne les premiers épisodes psychotiques, la clozapine est traditionnellement réservée aux patients qui ne répondent pas ou qui sont intolérants à au moins deux essais d'antipsychotiques de première ligne. Cependant, des recherches récentes suggèrent que son utilisation précoce pourrait être bénéfique pour certains sous-groupes de patients présentant un risque élevé de résistance au traitement ou des symptômes particulièrement sévères (82)comme le **risque suicidaire**. L'introduction rapide de la clozapine dans ces cas peut contribuer à une meilleure réponse symptomatique et à une atténuation du risque de chronicité(83).

L'efficacité de la clozapine dans les premiers stades de la psychose est soutenue par des études (84) suggérant que des interventions précoces et agressives peuvent modifier favorablement la trajectoire de la maladie.

L'ajustement de la dose de clozapine dans les premiers stades de traitement est particulièrement délicat en raison des métabolismes atypiques pour les enzymes CYP450, qui peuvent influencer considérablement les niveaux plasmatiques du médicament(85). La pharmacogénétique peut jouer un rôle crucial dans l'identification des patients à risque de ces métabolismes atypiques, permettant ainsi une personnalisation plus poussée du traitement

Les avantages potentiels de la clozapine dans les psychoses débutantes doivent être soigneusement pesés contre les risques d'effets secondaires. Cela nécessite une approche équilibrée et fondée sur des preuves pour intégrer ce puissant antipsychotique dans le traitement des premiers épisodes psychotiques. Des critères cliniques et pharmacogénétiques clairement définis pour l'initiation précoce de la clozapine pourraient ainsi améliorer sa prescription et le pronostic des patients souffrant de psychose débutante.

Notre étude évalue l'efficacité des modèles pharmacocinétiques de la clozapine à travers leur performance prédictive sur des données externes, et examine l'amélioration de l'optimisation du traitement via la prévision bayésienne. Sept modèles ont été analysés, montrant des performances prédictives limitées, avec un seul modèle répondant aux critères d'acceptabilité. La prévision bayésienne a significativement amélioré la performance prédictive des modèles.

L'approche bayésienne, en contexte de modélisation pharmacocinétique, fait référence à l'utilisation du théorème de Bayes (86)pour mettre à jour la probabilité de l'efficacité d'un traitement en fonction de nouvelles données. Le théorème de Bayes permet de combiner des connaissances préalables (a priori) avec des données actuelles pour obtenir une estimation améliorée (a posteriori).

En pharmacocinétique, cela implique l'ajustement de modèles basés sur des concentrations mesurées de médicament dans le corps pour prédire comment le médicament sera distribué, métabolisé, et éliminé chez un patient donné. L'approche bayésienne peut être utilisée pour personnaliser le dosage d'un médicament (comme la clozapine mentionnée) en prédisant la concentration qui sera atteinte dans le sang d'un patient à partir d'une dose spécifique.

En ce qui concerne l'amélioration de la prise en charge des psychoses débutantes, cet article ouvre des perspectives importantes. La capacité de personnaliser le traitement antipsychotique grâce à des outils pharmacocinétiques avancés, tels que les modèles PK et la prévision bayésienne, représente un pas en avant dans la prise en charge individualisée des patients.

L'approche utilisée dans l'article permet une meilleure compréhension et prédiction des niveaux plasmatiques de clozapine, ce qui pourrait potentiellement réduire le délai avant l'initiation d'un traitement à la clozapine chez les patients présentant des symptômes résistants ou des métabolismes

atypiques liés aux enzymes CYP450. Cette réactivité accrue est cruciale, car l'attente prolongée et les échecs successifs de traitement peuvent avoir des conséquences délétères sur l'évolution de la maladie, notamment en augmentant le risque de chronicité, de dysfonctionnement social et professionnel, et de comportements suicidaires.

La mise en œuvre de la prévision bayésienne dans la pratique clinique peut permettre une titration plus précise et rapide de la clozapine, minimisant les risques liés à sa toxicité tout en exploitant pleinement son potentiel thérapeutique. Cela pourrait également signifier que les patients ayant des métabolismes atypiques pour les CYP450, qui sont susceptibles de mal réagir aux antipsychotiques standards, pourraient bénéficier plus tôt d'une thérapie plus adaptée à leur profil biologique, réduisant ainsi le temps d'exposition à des symptômes non contrôlés.

L'optimisation du traitement par la clozapine à l'aide de modèles PK et de la prévision bayésienne pourrait ainsi représenter une avancée significative dans la prise en charge des troubles schizophréniques résistante dès les premiers stades. Cela permettrait une intervention thérapeutique personnalisée et dynamique, adaptée aux réponses individuelles des patients, avec l'objectif ultime d'améliorer les issues cliniques et de réduire la charge globale de la maladie.

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Towards Precision Dosing of Clozapine in Schizophrenia: External Evaluation of Population Pharmacokinetic Models and Bayesian Forecasting

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Background: Therapeutic drug monitoring and treatment optimization of clozapine are recommended, owing to its narrow therapeutic range and pharmacokinetic (PK) variability. This study aims to assess the clinical applicability of published population PK models by testing their predictive performance in an external data set and to determine the effectiveness of Bayesian forecasting (BF) for clozapine treatment optimization.

Methods: Available models of clozapine were identified, and their predictive performance was determined using an external data set (53 patients, 151 samples). The median prediction error (PE) and median absolute PE were used to assess bias and inaccuracy. The potential factors influencing model predictability were also investigated. The final concentration was reestimated for all patients using covariates or previously observed concentrations.

Results: The 7 included models presented limited predictive performance. Only 1 model met the acceptability criteria (median PE $\leq \pm 20\%$ and median absolute PE $\leq 30\%$). There was no difference between the data used for building the models (therapeutic drug monitoring or PK study) or the number of compartments in the models. A tendency for higher inaccuracy at low concentrations during treatment initiation was observed. Heterogeneities were observed in the predictive performances between the subpopulations, especially in terms of smoking status and sex. For the models included, BF significantly improved their predictive performance.

Conclusions: Our study showed that upon external evaluation, clozapine models provide limited predictive performance, especially in subpopulations such as nonsmokers. From the perspective of model-informed prediction dosing, model predictability should be improved using updating or metamodeling methods. Moreover, BF substantially improved model predictability and could be used for clozapine treatment optimization.

Key Words: pharmacokinetics, Bayesian forecasting, external evaluation, therapeutic drug monitoring, treatment optimization

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INTRODUCTION

Schizophrenia is a severe neuropsychiatric disorder that affects approximately 1% of the world's population, making it the most widespread form of psychosis in adults. Its consequences can be dramatic, and 40% of people with schizophrenia will attempt suicide.[1] Although treatments such as antipsychotics exist, they are only effective for 30%–60% of patients.[2] Dose personalization of these treatments for each patient remains very challenging because the dose required to achieve the optimal concentration varies substantially.

Clozapine is a tricyclic dibenzodiazepine neuroleptic that can be highly effective for patients with schizophrenia who do not respond to other antipsychotics.[3] Furthermore, it is the only second-generation antipsychotic drug approved to minimize the risk of suicide in patients with a history of schizophrenia.[4] However, clozapine has a narrow therapeutic range (350–600 ng/mL),[5] with significant inter- and intraindividual variability in serum concentrations for a given dose, partly due to its complex metabolism.[6] Clozapine undergoes first-pass metabolism and is metabolized by CYP1A2 and CYP3A4 to norclozapine and N-desmethylclozapine.[7] Thus, routine therapeutic drug monitoring (TDM) of clozapine is recommended to ensure its safety and avoid toxic adverse events.[8] In this context, clozapine pharmacokinetics (PK) have been extensively evaluated,[9] and several population PKs (popPK) models have been developed because plasma clozapine levels have been shown to be correlated with its clinical effects.[10]

The use of popPK models to guide molecule dose adjustment has proven efficient and is extensively used for molecules requiring individual treatment optimization.[11] In addition, a few drug concentration measurements can guide dosage adjustments by integrating the popPK model with the Bayesian forecasting (BF) method, reestimating the individual parameters of each patient using previous clinical

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TABLE 1. Literature Review Summary

Study (Publication yr) (Ref)	Country (Single/ Multiple Sites)	No. of Patients (Male/ Female)	No. of Samples (Sample Type)	Pathology	Software	No. of Compartments of the Model	Covariates Tested	PK Parameters and Formula (Clozapine)			IIV (%)	Residual Error
Li et al (2012)20	China (multiple)	162 (74/88)	809 (pk study)	Schizophrenia (n = 162)	NONMEM	One	Sex, age, weight, smoking	CL/F	21.9 L/h	NS females	42.9	52.9 ng/mL 26.60%
									26.46 L/h	NS males		
									38.37 L/h	S males		
									31.76 L/h	S females		
								V/F	526 L		65.7	
								Ka*	1.3 h^{-1}		None	
Shang et al (2012)19	China (multiple)	198 (125/73)	1391 (TDM data)	Schizophrenia (n = 180), healthy (n = 18)	NONMEM	Two	Sex, age, smoking, weight	Cl/F	21.9 L/h	NS females	45.1	28.40%
									31.1 L/h	NS males		
									37.0 L/h	S males		
								Q/F	83.3 L/h		None	
								V1/F	314 L		32.7	
								V2/F	272 L		90.3	
								Ka	1.3 h^{-1}		145.6	
								Tlag	0.245 h		None	
Ismail et al (2012)16	Canada (single)	391 (278/113)	1142 (TDM data)	Schizophrenia (n = 391)	NONMEM	One	Sex, age, height, weight, galenic formulation	Cl	36.7 L/h	Males	44.5	178,4 ng/mL
									27.0 L/h	Females		
								V*	950 L		93.2	
								Ka	0.80 h^{-1}			
Olmos et al (2019)21	Uruguay (single)	98 (76/22)	171 (pk study)	Schizophrenia (n = 98)	NONMEM	One	Smoking, age, sex, caffeine, brands, comedication	Cl/F	28.1 L/h	NS	43.3	9.54%
									36.5 L/h	S		
								V*	750 L			
								Ka*	1.24 h^{-1}			
Dailly et al (2002)18	France (multiple)	23 (14/9)	83 (TDM data)	Schizophrenia (n = 23)	NONMEM	One	Age, weight, height, CYP1A2 activity, daily dose	CL	32.3 L/h		27.1	33.30%
								V	272 L		22.5	
								Ka*	1.30 h^{-1}		None	
Jerling et al (1997)22	Sweden (single)	241 (159/82)	391 (TDM data)	Schizophrenia (n = 241)	NPML	One	Sex, age, CYP1A2 activity	Cl/F	39.9 L/h	Females	None	None
									47.9 L/h	Males		
								V/F	564 L	Females	None	
									719 L	Males		
								Ka	1.24 h^{-1}	Females	None	
									1.37 h^{-1}	Males		

(*continued on next page*)

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TABLE 1. (*Continued*) Literature Review Summary

Study (Publication yr) (Ref)	Country (Single/ Multiple Sites)	No. of Patients (Male/ Female)	No. of Samples (Sample Type)	Pathology	Software	No. of Compartments of the Model	Covariates Tested	PK Parameters and Formula (Clozapine)			IIV (%)	Residual Error
Ng et al (2009)17	Canada (single)	197 (138/59)	519 (TDM data)	Schizophrenia (n = 193), other (n = 4)	NONMEM	One	Sex, age, weight, smoking, dosage formulation	Cl	18.0 L/h	NS females	60.8	11.50%
									52.46 L/h	NS males		
									24.0 L/h	S females		
									28.46 L/h	S males		
								F	0.817			
								V/F*	7.00 L/kg		131.5	
								Ka	0.14 h^{-1}		None	

*Fixed value from the literature.

CL, clearance; Ka, absorption rate constant; Q, intercompartmental clearance; NONMEM, nonlinear mixed effect modeling; NPML, nonparametric maximum likelihood; NS, nonsmoker; pk study, pharmacokinetics study; S, smoker; Tlag, lag time of absorption; V, volume of distribution; V1, volume of distribution of the central compartment; V2, volume of distribution of the peripheral compartment.

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observations.[12] Although various popPK models for clozapine have been published, to the best of our knowledge, very few have been confronted with external evaluation and many have only undergone internal evaluation.[9] However, the literature has shown that it is not enough to perform an internal evaluation of predictive models; it is essential to confirm the predictive performance of models on external data to generalize them to different individuals outside the development set.[13] This allows the creation of an individualized therapeutic approach for different populations. Such models must guide decision making in treatment optimization and ultimately improve patient outcomes.[13] Therefore, this study aimed to assess the application of previously published models by testing their predictive performance in an external data set and to determine the potential benefits of BF for clozapine treatment optimization.

MATERIALS AND METHODS

Search Methods and Inclusion Criteria

In May 2020, we performed a systematic literature search of the PubMed/Medline database for all published popPK models of clozapine. The query used was "clozapine [Ti] AND (popPKs OR model)." To be included in this review, the study had to meet all the following criteria: (1) the models should be popPK models of clozapine, (2) all the parameters of the model had to be explicitly described, such as all the population equations, and (3) the publication was written in English. Articles were excluded if they were reviews, animal studies, or in vitro studies. To be included in the study of the impact of BF on the model's predictive performance, models needed to have their complete error model defined in the article.

External Evaluation Data

Patients and Treatment

Data were retrospectively collected from hospitalized patients who had schizophrenia or severe schizophrenic disorders and were followed up in the psychiatric unit of the Conception University Hospital, Marseille, France, from July 6, 2011 to August 10, 2013. This study was approved by the Marseille university hospital committee as a retrospective, noninterventional, and anonymous study, following the European GDPR standards (RGPD/AP-HM N° 2021-85). The patients enrolled in this study were treated with clozapine and received at least one dose of clozapine for TDM. For all patients, TDM data (sample time, time of last dose, dosing regimen), demographic data (age, weight, height, smoking status, sex), and biological data were collected. Genotype data were unavailable and were not included in the model evaluation.

Treatment with clozapine was initiated with a titration phase, lasting 15–20 days on average, with a regular increase in the dose. This increase, by 25–50 mg every 2 or 3 days, occurred according to the patient's clinical response to treatment. The titration phase ended when the patient reached the usual efficient dosing regimen (300–400 mg). The daily dose was adapted using TDM (through concentrations). The exact time of blood sampling was recorded by the attending medical staff, and the samples were transported to the pharmacological laboratory within 5 hours. Clozapine concentrations were quantified using a validated high-performance liquid chromatography method with UV detection (245 nm) according to the EMA guidelines. The limit of quantification was 25 ng/mL with a bias and inaccuracy of $<20\%$, and the assay was linear up to 1000 ng/mL. When higher concentrations were observed, the samples were diluted before reanalysis.

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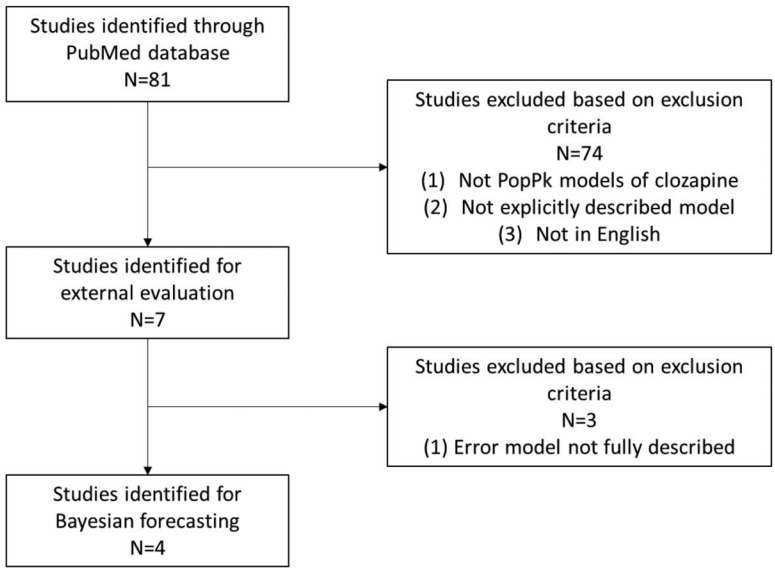


FIGURE 1. Overview of the strategy used in the literature search. N: Number of articles returned by the search.

Model Evaluation

Prediction-Based Diagnostics

The external evaluation was conducted using an EXACTCURE (Nice, France) medical device (ANSM registration: DM1SM202000483), which was developed in the Python language.[14] The final popPK models were simulated based on the formulae and parameters reported for each of the included popPK publications. External evaluation was performed without the additional fitting of the model to the data.

Prediction error (PE) and absolute PE were used to assess the predictive performance of the models. PE and absolute PE were determined using the following equations:

$$PE(\%) = \frac{Cpred - Cobs}{Cobs} * 100$$

$$APE(\%) = |PE| * 100,$$

where C_{pred} and C_{obs} are the predicted and observed concentrations, respectively.

The median PE (MDPE) and median APE (MADPE) were used as measures of bias and inaccuracy, respectively.

1. The bias (ie, the direction and the size of the deviation from the observed concentration) of model predictions is given for the i^{th} individual and j^{th} blood sample, using the MDPE:

$$MDPE(\%) = MEDIAN(PE(\%)(ij)).$$

1. The inaccuracy (ie, the size of a typical miss) of model predictions is given for the ith individual and jth blood sample using the MADPE:

$$MADPE(\%) = MEDIAN(APE(\%)(ij)).$$

An MDPE between −20% and 20% and a MADPE ≤30% are considered acceptable criteria for bias and inaccuracy.[15]

Bayesian Forecasting

The last concentration was calculated for all patients using covariates only (a priori prediction) or using all previously observed clozapine concentrations (Bayesian estimation) according to the "all data" method. This method estimates the last concentration by calibrating the individual PK parameters with a maximum a posteriori Bayesian method based on all previous concentrations. The predicted concentrations estimated using the a priori and Bayesian approaches were then compared.

We calculated the individual prediction error (IPE) and individual prediction absolute error (IPAE) as indicators of the BF efficiency as follows:

$$IPE(\%) = \frac{IPRED - OBS}{OBS} * 100$$

TABLE 2. Characteristics of the External Evaluation Data Set

Characteristics	Number or Mean ± SD	Median (Range)
No. of patients (male/female)	53 (41/12)	NA
No. of samples	151	NA
No. of samples per patient	2.77 (±3.90)	1 (1–20)
Age (yr)	38.66 (±11.51)	37 (19–66)
Weight (kg)	81.21 (±19.20)	80 (47–122)
Height (cm)	172.92 (±8.54)	175 (153–185)
Concentration (mg/L)	381 (±296)	287 (36–1504)
Dose (mg)	224.29 (±129.90)	200 (25–625)
Smoker (yes/no)	32/21	NA

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TABLE 3. Results of the External Evaluation for 7 Published popPK Models (MDPE/MADPE in %)

Reference	MDPE	MADPE
Li et al[20]	19.2	34.5
Shang et al[19]	15.9	31.2
Ismail et al[16]	11.9	35.8
Olmos et al[21]	11.7	32.5
Dailly et al[18]	4.5	31.3
Jerling et al[22]	−19.0	29.4
Ng et al[17]	38.5	43.9

$$IAPE(\%) = \frac{IPRED - OBS}{OBS} \text{V} 100,$$

where *IPRED* is the individual prediction of the last observation and *observation (OBS)* is the last observation.

We also recalculated the MDPE and MADPE after BF.

RESULTS

Published Models

After a literature search, 7 models were identified (Fig. 1).[16–22] Two studies were conducted in China, 2 in Canada, and the others in Sweden, France, and Uruguay (Table 1). All but one of the studies included more than 100 subjects.[18] All the models followed linear first-order kinetics. Clozapine was described using 1-compartmental models in 6 studies and as a 2-compartmental model in 1 study. In these compartmental models, the absorption phase was described in 3 models using a fixed constant of absorption (Ka). The volume of distribution (V) was fixed in 3 models, unlike clearance, for which interindividual variability was estimated in all models. Overall, 10 different covariates were tested in 7 published models (sex, age, weight, smoking status, galenic formulation, caffeine intake, brands, comedication, CYP1A2 activity, and daily dose), and 3 were included in parameter estimation: smoking status (n = 4), sex (n = 5), and weight (n = 1) (Table 1).

Patients

The external evaluation data set comprised 151 samples from 53 patients. Demographic data are summarized in Table 2. Patients ranged in age from 19 to 66 years and weight from 47 to 122 kg. There were 41 men and 12 women, and smoking status was reported for each patient (32 smokers). Out of this data set, 21 patients who had more than 1 sample were selected for BF, with the number of prior samples ranging from 1 to 11. Concentrations were monitored at both the titration phase and the steady state.

Model Evaluation

Prediction-Based Diagnostics

All 151 samples were used to evaluate the predictive performance of the models. The MDPE ranged from 4.5% to 38.5%, and the MADPE ranged from 29.4% to 43.9%. First, only the model developed by Jerling et al[22] met the aforementioned criteria (MDPE ≤ ±20% and MADPE ≤30%). Most models had an MDPE ≤ ±20% and MADPE ≤40% (Table 3). Figure 2 shows the box plots of the PE for all 7 published models.

To assess the influence of the model's structure, the MDPE and MADPE were compared between the 1- and 2-compartment models. The MDPE/MADPE for the 1-compartment models was 11.8% and 35.5%, respectively, whereas the MDPE/MADPE for the 2-compartment model was 15.9% and 31.2%, respectively. Furthermore, the MDPE and MADPE were compared between models built with TDM data or data from full-profile PK studies. No impact was

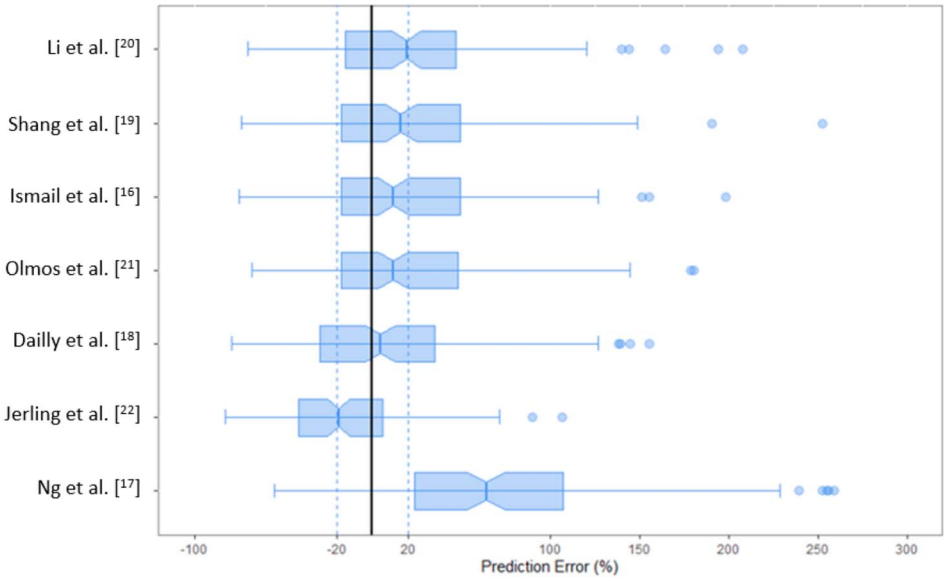


FIGURE 2. Box plots of the PEs for the 7 published popPK models. The black solid lines and blue dotted lines are reference lines indicating the PE% of 0% and ±20%, respectively.

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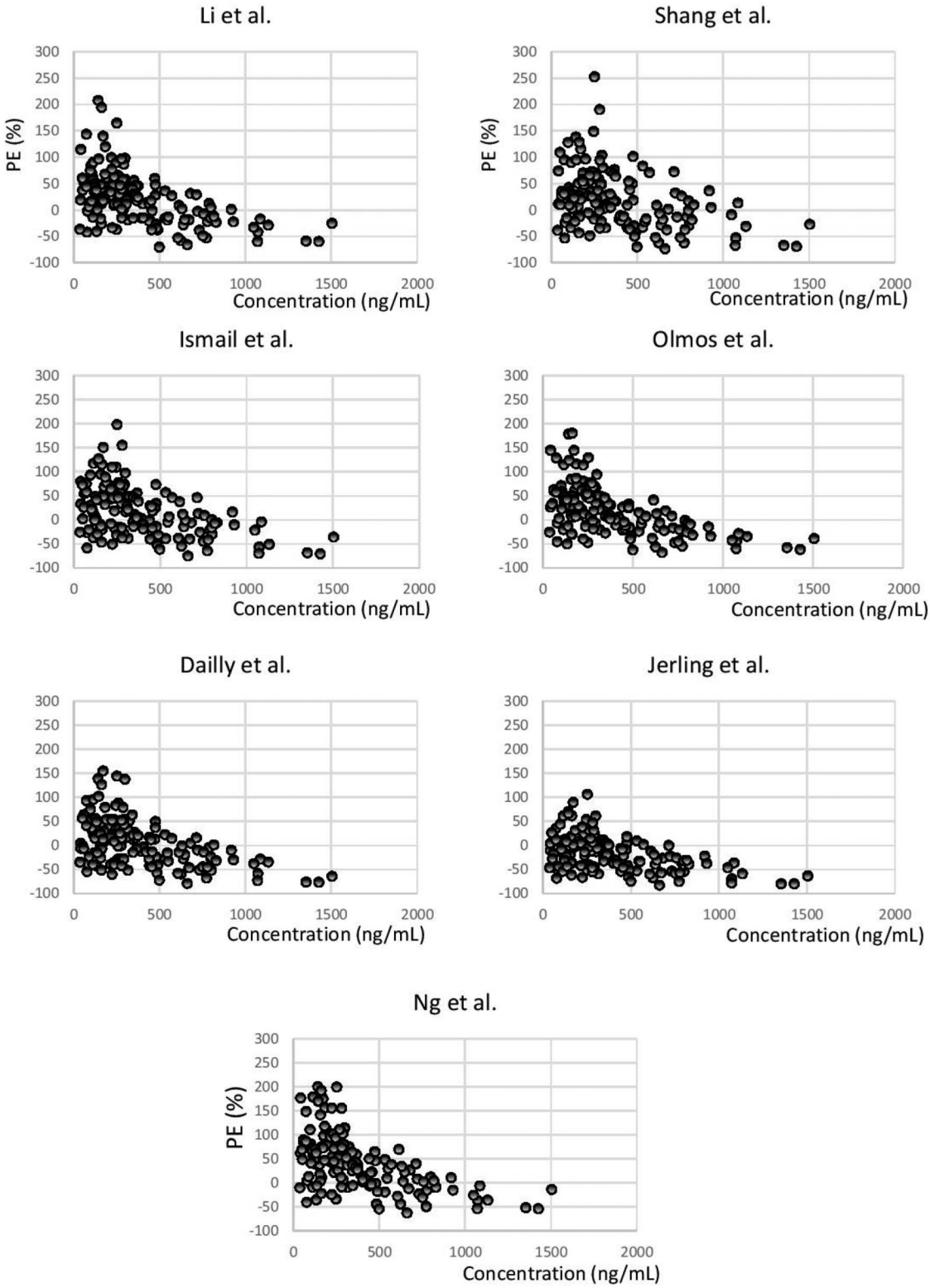


FIGURE 3. Plots of the PEs in percentage versus the observations in nanograms/milliliters for each of the 7 published models.

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TABLE 4. Results of Bayesian Forecasting Study

Reference	MDPE A Priori	MADPE A Priori	MDPE A Posteriori	MADPE A Posteriori
Li et al[20]	33.3	43.0	9.3	18.0
Shang et al[19]	12.9	21.2	0.5	10.5
Olmos et al[21]	23.8	25.0	6.2	27.0
Dailly et al[18]	4.6	18.6	−0.6	11.4

External evaluation was performed before (a priori) and after (a posteriori) the use of the "all data" method. The MDPE/MADPE values were calculated as a percentage.

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observed on the predictive performance of these models. For TDM data studies, the MDPE/MADPE values were 11.31% and 35.80%, respectively, whereas for full-profile PK studies, the MDPE/MADPE was 19.7% and 33.5%, respectively.

Predictor errors were plotted for each model versus the observations to visualize whether there was a difference in the predictive performance according to concentration (Fig. 3). A higher inaccuracy in the low-concentration predictions was observed. Furthermore, low concentrations tended to be predicted with a positive bias, whereas high concentrations tended to be predicted with a negative bias. In addition, goodness-of-fit plots were also provided (see **Figure 2**, **Supplemental Digital Content**, http://links.lww.com/TDM/A573).

To assess the impact of the patient's demographic and biological characteristics on the models' predictive performances, the MDPE and MADPE were also calculated for different subgroups of the population: body mass index (BMI) >30 or <30, smokers or nonsmokers, and males or females. Heterogeneities were found in the prediction performance for several models due to the population subgroup (Table 5).

Bayesian Forecasting

To assess the impact of using BF in the personalization of clozapine treatment, all prior samples were used to estimate the last observation for each of the 21 patients included in the data set. Only 4[18–21] of the 7 models could be included because of a lack of information on the error models in the 3 others. The MDPE and MADPE were recalculated a priori (using only model covariates) and a posteriori, respectively. BF significantly improved the predictive performance of the models, and all 4 models reached the acceptability criteria for MDPE and MADPE (Table 4). Bias and inaccuracy were especially improved in the low- and high-concentration ranges, as in models that already had a low bias (see **Figure 1**, **Supplemental Digital Content**, http://links.lww.com/TDM/A572).

DISCUSSION

Clozapine was the first effective atypical antipsychotic for patients with resistant schizophrenia.[3] TDM and treatment optimization are highly recommended for this drug because of its very narrow therapeutic range and large inter- and intra-PK variability. The equilibration of clozapine treatment is complex, and many patients have issues with reaching therapeutic concentrations. Modeling and simulation methods have shown significant advantages in many therapeutic areas in supporting dosing regimen selection for patients[23] but are not frequently used in psychiatry. In our study, we aimed to analyze available popPK literature for clozapine and assess the possibilities of performing BF and model-informed precision dosing (MIPD) for this molecule.

To the best of our knowledge, this is the first study that evaluated the predictive performance of published popPK models of clozapine in patients with schizophrenia using an independent external evaluation data set. Compared with other molecules that require precision dosing, such as antiepiletics or antimicrobials, we observed that only a few popPK models of clozapine had been developed. Indeed, in the psychiatric field, numerous molecules require precision dosing; however, even those used for several decades, such as lithium, do not have many popPK models published.[24] Concerning valproic acid, most models have been developed for patients with epilepsy and not for psychiatric populations.[25] Although it has been proven that the external evaluation of models is an important additional feature and is even necessary for use in patient dose personalization in clinical settings,[26] few popPK models developed in psychiatry have been externally evaluated. The popPK models of clozapine identified in the literature used only internal evaluation to test their predictive performance.

In the present study, an important variability was observed in the predictive performance of the studied models, and most of them presented limited results. Among the available popPK models of clozapine, only 1 met a priori the criteria of acceptability (MDPE $\leq \pm 20\%$, MADPE $\leq 30\%$) in our data set.[22] All models had an acceptable bias, but only 1 had sufficiently high inaccuracy. Studying the details of the predictions, we found a tendency of higher prediction inaccuracy at low concentrations that were most often overpredicted. This issue could be because most models[16–19,21] were built only or mainly on steady-state data; therefore, only a few low concentrations have been used to develop these models. This could explain why these models were generally better at predicting average concentrations than the lower concentrations observed during the initiation phase of treatment. Another explanation could be through the analytical methods used, as higher bias and inaccuracy could be expected at low concentrations close to the limit of quantification. Moreover, we observed a tendency to underpredict high concentrations in the goodness-of-fit plots (see **Figure 2**, **Supplemental Digital Content**, http://links.lww.com/TDM/A573). This could be explained by the fact that some variability factors were not considered in the evaluated models. For example,

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TABLE 5. Results of the External Evaluation for the 7 Published popPK Models (MDPE/MADPE in %) on Subgroups of the Population: BMI >30 and <30, Smokers and Nonsmokers, Male, and Female

Reference	MDPE BMI <30	MDPE BMI >30	MADPE BMI <30	MADPE BMI >30	MDPE Smoker	MDPE Non-smoker	MADPE Smoker	MADPE Non-smoker	MDPE Male	MDPE Female	MADPE Male	MADPE Female
Li et al[20]	19.2	22.9	37.2	28.6	20.3	13.8	31.6	37.8	20.0	17.7	37.8	25.7
Shang et al[19]	9.3	26.5	26.5	36.7	28.7	−5.3	36.3	26.6	8.4	56.4	28.7	58.4
Ismail et al[16]	5.0	18.3	35.8	36.8	40.2	−15.1	45.2	24.7	4.7	34.7	35.5	35.8
Olmos et al[21]	19.0	6.4	32.8	30.1	12.9	10.2	32.7	31.0	26.6	1.8	38.8	20.2
Dailly et al[18]	1.4	10.4	34.7	29.0	16.1	−6.6	33.5	29.7	2.9	9.0	35.0	24.6
Jerling et al[22]	−19.7	−12.2	30.5	21.7	−2.1	−36.5	23.3	37.5	−19.5	−7.6	31.1	21.9
Ng et al[17]	41.1	27.5	47.5	35.0	46.3	25.1	47.3	38.5	40.0	31.7	47.1	35.7

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the phenomenon of clozapine metabolism saturation is not incorporated even in models including norclozapine,[27] like the inflammation status, which has been proven to inhibit clozapine metabolism.[28]

We compared the impact of model structure on predictability and found no difference in predictive performance. Of the 7 models we evaluated, only 1 was a 2-compartment model.[19] This can be explained by the fact that building a 2-compartment model requires more data to fit parameters with reasonable variability. Attempts to identify the parameters in the absorption and distribution phases were pursued for some models, but a lack of data available during these phases forced pharmacometricians to fix certain values. This led to 3 studies fixing their absorption constant and 3 studies fixing their volume of distribution. This is a recurrent issue for clozapine, as its TDM shows inherent limitations for model building because it was mainly performed on residual concentrations. Therefore, there was a lack of samples collected during the absorption and distribution phases. However, we found that the 2-compartment model was not the best predictor in our study, even though it was built on 4 different data sets, including TDM and PK study data on all phases of clozapine PKs.

We also compared the predictability of the models according to the covariates included. As already noted in the literature, the covariates of interest for clozapine are mainly smoking status and gender,[29] as they strongly impact its metabolism. Indeed, smoking status and sex are known to modify CYP1A2 activity. CYP1A2 activity is greater in smokers than in nonsmokers, and women have a lower CYP1A2 activity than men.[30] This impacts clozapine clearance, as it is primarily metabolized by this cytochrome. Of the studied models, only 3 included both smoking status and sex covariates,[17,19,20] 2 included sex alone,[16,22] and 1 included smoking status alone.[21] No clear association between these covariates and improved predictability was found in our study. Indeed, even our best model[22] did not include smoking as a covariate because it did not have smoking information in its building data set. Conversely, our least predictive model included smoking, sex, and weight as covariates; this was the only model that included weight. Weight is not a common covariate for clozapine PKs; however, some studies have found that the increase in weight during clozapine treatment is associated with an increase in the plasma concentration of clozapine due to a decrease in its clearance.[31] It would be interesting to further investigate this covariate in future studies, as weight gain is a known side effect of clozapine treatment.

Prediction-based diagnostics showed a lack of predictability in some subpopulations, which could limit the use of these models in clinical practice. The variation in predictability was mainly due to sex and smoking status. Most of the models presented a higher bias in smokers than in nonsmokers. Indeed, we observed an overprediction of clozapine concentrations in this subpopulation (Table 5) in 6 models.[16–21] This could be explained by the lack of or insufficient representation of enzymatic induction due to tobacco. This is an important issue in model prediction because the psychiatric population is mainly composed of smokers. Conversely, our best model did not meet the acceptability criteria for the nonsmoker population. In conclusion, clozapine models are quite accurate when confronted with external evaluations, but none of the studied models met the acceptability criteria for every subpopulation.

We also assessed the impact of BF on model predictability. BF is already used in the clinical context for drug dose optimization and is adapted for individual predictions.[32] Indeed, tools for precision medicine using prior concentrations to personalize simulations have shown efficiency in treatment personalization because they significantly improve prediction despite interindividual variability. Our BF study highlights a potential interest in its use in clozapine treatment optimization. The predictive performances of the 4 models that could be included in the study were substantially improved after BF, making them meet the set acceptability criteria. Using the improvement in predictability induced by BF at low concentrations for treatment optimization would be very efficient during treatment initiation (see **Figure 1**, **Supplemental Digital Content**, http://links.lww.com/TDM/A572). The use of more than 1 concentration can help estimate the end of the titration phase. However, our data set for the Bayesian study was limited. We could not determine the

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influence of the number of prior concentrations on improving predictability because we did not have a wide enough range of patients and number of prior samples.

CONCLUSIONS

In conclusion, published clozapine popPK models were evaluated using an independent data set and compared with BF methods in this study. Currently, optimization of clozapine treatment is not widely performed using MIPD. In psychiatry, many molecules such as clozapine require precise dosing, and popPK modeling can help patients reach therapeutic concentrations faster and safer. However, our study showed that the available popPK models had limited predictive performance for use in MIPD, especially on specific subpopulations. Consequently, it would be interesting to first improve PK models predictability of clozapine on the population levels, with methodologies such as meta modeling. Moreover, adding covariates would allow for a better predictability and transposability of the models for every subpopulation. On the individual level, BF seems to be an efficient tool for optimizing dosing adjustments.

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Chapitre 2 : Impact de la motivation dans les premiers épisodes psychotiques

A- Définition clinique de la motivation

B- Motivation et premiers épisodes psychotiques

C- Precision-medicine findings from the FACE-SZ cohort to develop motivation-enhancing programs in real-world schizophrenia

A- Définition clinique de la motivation

La motivation est un processus psychologique et neurobiologique qui incite un individu à agir vers un but spécifique. Ce processus est complexe et implique diverses structures cérébrales, systèmes de neurotransmetteurs, et mécanismes de récompense(87). Elle est fondamentale pour la survie, car elle oriente les comportements vers la satisfaction des besoins essentiels et la réalisation d'objectifs personnels.

La motivation joue notamment un rôle crucial dans le syndrome négatif des troubles schizophréniques, affectant profondément la vie des patients, qu'il convient donc de prendre en charge(88). Comme nous l'avons évoqué dans l'introduction, le syndrome négatif se caractérise par une diminution ou une absence de capacités à initier des plans, des émotions, ou à prendre plaisir dans la vie quotidienne. Les symptômes incluent l'apathie, le retrait social, le manque d'expression émotionnelle, et une incapacité à ressentir du plaisir, phénomènes qui sont étroitement liés à la motivation ou plutôt à son absence. Cela conduit à des difficultés significatives dans la gestion des activités quotidiennes, les relations sociales et la capacité à mener une vie indépendante.

Au cœur du système de motivation se trouve le système de récompense du cerveau, un ensemble de structures cérébrales impliquées dans la perception du plaisir, la prise de décision, et la recherche de récompense(89). Les composants clés de ce système incluent le cortex préfrontal, le noyau accumbens, l'amygdale, et l'hippocampe. Ces régions interagissent pour évaluer les stimuli, déterminer leur valeur de récompense, et ainsi motiver l'individu à effectuer les actions nécessaires pour obtenir cette récompense.(90)

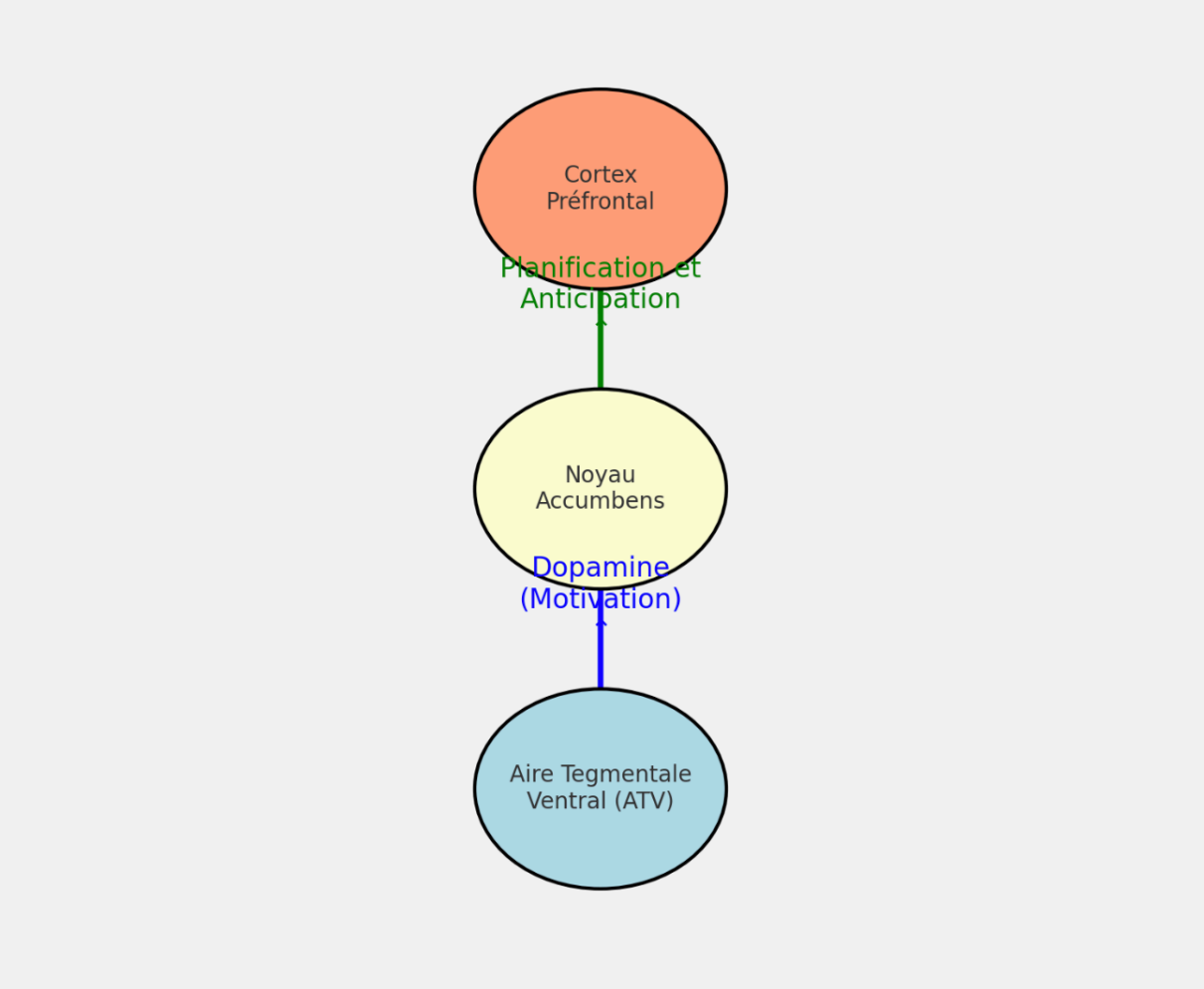


Schéma simplifié mettant en évidence les principales parties du cerveau impliquées dans la motivation via le système de la récompense :

Cortex Préfrontal : Responsable de la planification complexe, de la prise de décision, et de l'anticipation des récompenses. Il joue un rôle dans la motivation en évaluant les actions à prendre pour atteindre un objectif désiré.
Noyau Accumbens : Joue un rôle central dans la voie de la récompense et est impliqué dans la motivation liée aux récompenses. Il reçoit des signaux du cortex préfrontal et de l'ATV.
Aire Tegmentale Ventrale (ATV) : Source majeure de dopamine, un neurotransmetteur lié à la motivation, au plaisir et à la récompense. L'ATV envoie de la dopamine au noyau accumbens, stimulant ainsi la motivation.
Les flèches bleues et vertes montrent respectivement le flux de dopamine et l'influence du cortex préfrontal sur le noyau accumbens.

Dans le contexte des premiers épisodes psychotiques, un dysfonctionnement dans ces régions ou dans les voies dopaminergiques (91)peut contribuer au manque de motivation souvent observé(92). Cela peut être dû à une altération de la libération de dopamine, affectant ainsi l'anticipation de la récompense et la motivation à entreprendre des actions.

Des altérations dans les circuits cérébraux liés à la récompense et à la motivation, notamment dans les régions préfrontales et le striatum, peuvent réduire la capacité des patients à anticiper le plaisir ou à être motivés par des récompenses, notamment en situation sociale(93). Cela rend difficile l'engagement dans des activités ou des objectifs qui sont normalement sources de satisfaction.

Le neurotransmetteur le plus étroitement associé à la motivation est la dopamine. La dopamine est sécrétée dans différentes parties du cerveau et joue un rôle crucial dans la régulation du plaisir, de la récompense, et de la motivation(94). Une augmentation de la dopamine dans certaines zones du cerveau est associée à une augmentation de la motivation à poursuivre des activités jugées gratifiantes(95).

En psychiatrie, la motivation est souvent définie à travers le prisme de son influence sur le comportement et le fonctionnement mental d'un individu, notamment en ce qui concerne sa capacité à initier, maintenir et orienter des actions vers des objectifs. Elle est considérée comme un symptôme pouvant être affecté dans diverses conditions psychiatriques.

La prise en charge des symptômes négatifs, et particulièrement des déficits motivationnels, représente un défi majeur dans le traitement des troubles schizophréniques. Les médicaments antipsychotiques de première intention (aripiprazole, risperidone, olanzapine, quetiapne et amisulpride) dans les recommandations sont souvent moins efficaces contre les symptômes négatifs que contre les symptômes positifs (comme les hallucinations ou les idées délirantes)(96). Cela souligne l'importance de développer des stratégies thérapeutiques spécifiques, y compris des thérapies cognitivo-comportementales et des interventions psychosociales, pour améliorer la motivation et la fonction sociale.

Les recherches récentes soulignent l'importance des approches personnalisées et ciblées pour traiter le manque de motivation chez les patients atteints de troubles schizophréniques. Des techniques comme la remédiation cognitive, l'entrainement à la motivation et les thérapies centrées sur les objectifs montrent un potentiel pour améliorer l'engagement des patients dans des activités significatives, augmentant ainsi leur qualité de vie. Ces approches se concentrent sur le renforcement des compétences sociales, la gestion des objectifs et l'amélioration de la perception de la récompense.

Finalement, comprendre et traiter efficacement la motivation dans le syndrome négatif nécessite une approche globale qui prend en compte les besoins individuels du patient. Cela implique souvent une combinaison de médicaments, de thérapies comportementales et de soutien psychosocial, visant non

seulement à réduire les symptômes négatifs mais aussi à améliorer le fonctionnement général et le bien-être. L'accent mis sur la motivation dans le traitement des troubles schizophréniques reflète une évolution vers des soins plus holistiques, reconnaissant l'importance de la qualité de vie au-delà des symptômes traditionnels.

B- Motivation et premiers épisodes psychotiques

Lors des phases précoces des troubles, l'absence de motivation, ou avolition, est souvent moins visible que les symptômes positifs tels que les hallucinations ou les délires, mais elle a un impact profond sur le fonctionnement quotidien et la qualité de vie des patients(97).

Au début des troubles schizophréniques, l'absence de motivation peut se manifester par un désintérêt pour les activités sociales, scolaires ou professionnelles. Les jeunes adultes ou les adolescents, qui sont à l'âge typique de l'apparition des troubles schizophréniques, peuvent commencer à montrer un manque d'intérêt pour les études ou les loisirs, se retirer de leurs amis et de leur famille, et négliger leur hygiène personnelle et leur alimentation(98). Ces changements peuvent être mal interprétés comme de la paresse ou des comportements adolescents physiologiques, retardant le diagnostic et la prise en charge.

En résumé, l'absence de motivation dans les troubles schizophréniques débutants présente un défi pour la prise en charge de la maladie. Une détection et une intervention précoces peuvent non seulement atténuer les symptômes négatifs mais aussi améliorer de manière significative le pronostic à long terme pour les patients. Cela nécessite une approche multidisciplinaire qui intègre des interventions médicales, thérapeutiques, et de soutien psychosocial, soulignant l'importance de la collaboration entre les professionnels de santé, les patients, et leurs familles pour combattre efficacement les troubles schizophréniques.

Nous avons donc voulu réaliser un travail permettant de mieux appréhender cette problématique de la motivation concernant la prise en charge de la schizophrénie débutante.
Premièrement, en se concentrant sur les déficits de motivation, un aspect souvent sous-estimé du syndrome négatif des troubles schizophréniques, cette étude met en lumière l'impact profond de ces déficits sur le fonctionnement quotidien et la qualité de vie des patients. Comprendre les facteurs associés à ces déficits permet d'identifier des cibles thérapeutiques précises, ouvrant la voie à des interventions plus ciblées et potentiellement plus efficaces dès les premiers stades de la maladie.

Deuxièmement, en identifiant des facteurs modifiables associés aux déficits de motivation, tels que les troubles du sommeil, la dépression, ou encore la faible adhérence médicamenteuse, cette recherche souligne l'importance d'une approche holistique dans le traitement des premiers épisodes psychotiques.

Troisièmement, la mise en évidence de l'association entre déficits de motivation et consommation de substances telles que l'alcool et la nicotine incite à intégrer des programmes de prévention et de traitement des addictions dans les plans

de soin pour les patients souffrant de troubles schizophréniques. Cela est particulièrement pertinent dans le contexte des troubles schizophréniques débutants, où l'intervention précoce pourrait prévenir le développement de comportements addictifs et leur impact négatif sur la motivation et la qualité de vie.

Quatrièmement, cette étude fait écho à la littérature existante tout en explorant des domaines jusqu'alors peu étudiés en relation avec les déficits de motivation dans les troubles schizophréniques, comme **l'impact des antécédents de tentatives de suicide** ou les symptômes positifs. Cela enrichit notre compréhension globale de la maladie et offre de nouvelles perspectives pour des approches thérapeutiques innovantes. C'est le cas par exemple de la stimulation magnétique transcrânienne dont les premières études montrent un gain quant à la prise en charge du syndrome négatif dans la schizophrénie.

Enfin, cette recherche soutient l'idée que la prise en charge efficace des troubles schizophréniques, en particulier dans ses stades initiaux, nécessite une attention particulière aux symptômes négatifs tels que les déficits de motivation.

En se focalisant sur ces aspects dès le début, il est possible d'améliorer significativement les résultats à long terme pour les patients, en favorisant un meilleur fonctionnement social, professionnel, et une meilleure qualité de vie globale.

C- Precision-medicine findings from the FACE-SZ cohort to develop motivation-enhancing programs in real-world schizophrenia, publié dans The World Journal of Biological Psychiatry



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Precision-medicine findings from the FACE-SZ cohort to develop motivation-enhancing programs in real-world schizophrenia

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ORIGINAL INVESTIGATION

Precision-medicine findings from the FACE-SZ cohort to develop motivation-enhancing programs in real-world schizophrenia

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ABSTRACT

Background: In people with schizophrenia, major areas of everyday life are impaired, including independent living, productive activities, social relationships and overall quality of life. Enhanced understanding of factors that hinder real-life functioning is vital for treatments to translate into more positive outcomes.

Aim: The goal of the present study was to identify factors associated with motivation deficits in real-life schizophrenia, and to assess its contribution to impaired functioning and quality of life.

Methods: Based on previous literature and clinical experience, several factors were selected and grouped into factors potentially explaining motivation deficits. Some of these variables were never investigated before in relationship with motivation deficits.

Results: In 561 patients with schizophrenia of the national FACE-SZ cohort living in the community, 235 (41.9%) reported severe motivation deficits. These deficits were found to be significantly associated with impaired socially useful activities, psychological and physical quality of life (in almost all domains), alcohol use disorder (aOR = 2.141, $p = 0.021$), severe nicotine dependence (aOR = 2.906, $p < 0.001$) independently of age and sex. No significant association was found for body mass index, metabolic syndrome or physical activity level. In the second model, we identified the following modifiable factors associated with motivation deficits: history of suicide attempt (aOR = 2.297, $p = 0.001$), positive symptoms (aOR = 1.052, $p = 0.006$), current major depressive episode (aOR = 2.627, $p < 0.001$), sleep disorders (aOR = 1.474, $p = 0.024$) and lower medication adherence (aOR = 0.836, $p = 0.001$) independently of gender, current alcohol use disorder, second-generation antipsychotics and akathisia. No significant association was found for negative symptoms, childhood trauma and inflammation. These results were maintained after removing patients with schizoaffective disorders or those with major depressive disorder.

Interpretation: Motivation deficits are frequent and remain persistent unmet need in real-world schizophrenia that should be addressed in future guidelines. Based on our results, literature and clinical experience, we recommend to address in priority major depression, sleep, suicide, positive symptoms (when present and as early as possible) and medication adherence to improve motivation deficits of schizophrenia.

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1. Introduction

Motivation deficits have been observed in schizophrenia from the first clinical descriptions of Bleuler ('having no urge to do anything either on their own initiative or at the bidding of another') and Kraepelin ('loss of mastery on volition') (Foussias and Remington 2010). Motivation deficits are currently gathered under the name of 'avolition' and defined in the DSM-5 as 'a decrease in motivated self-initiated purposeful activities' (American Psychiatric Association. 2013). Motivation includes directional (approach or avoidance) and energetic aspects (vigor and persistence in pursuing an outcome) (Bromberg-Martin et al. 2010; Salamone et al. 2016). There is consensus that motivation deficits are central to schizophrenia physiopathology from the early prodromal phase to the chronic phase of the illness (Gupta et al. 2021; Strauss et al. 2021) and that these deficits are different from those seen in mood disorders (Yang et al. 2021). Motivation deficits were considered as the most central of the five negative symptoms domain (the others being alogia, blunted affect, social withdrawal, and anhedonia) in the 2005 NIMH Consensus Conference (Kirkpatrick et al. 2006). Their central role has been confirmed in a recent symptoms network analysis (Strauss et al. 2021). It is now well established that they strongly impact the functioning and quality of life of people with schizophrenia (Fulford et al. 2018; Galderisi et al. 2018; Mucci et al. 2021; Uchino et al. 2021). They may also limit the success of interventions targeting risky health behaviour including losing weight (McGinty et al. 2016; Weye et al. 2021), increasing physical activity level (Vancampfort et al. 2015; Stubbs et al. 2017) and addictions cessation (Cather et al. 2017).

Among aetiological factors explaining motivation deficits in schizophrenia, a long list of potential culprits was missing from previous works. First, it is now consensual that the simultaneous evaluation of negative and depressive symptoms is important to clarify the relative contribution of these two psychopathological domains to real-life functioning (Galderisi et al. 2014). A recent meta-analysis has found motivation deficits at the crossroad of negative and depressive syndromes (Krynicki et al. 2018). Major depression has been identified in one third of the schizophrenia patients and remains underdiagnosed and poorly treated (Fond et al. 2018; Etchecopar-Etchart et al. 2021). Second, sleep disorders are identified in more than an half of schizophrenia patients and may also favour motivation deficits (Meyer et al. 2020; Sunhary de Verville et al. 2021). Third, chronic inflammation has been identified in two thirds of patients with schizophrenia (Fond et al. 2021). This inflammation may decrease motivation via the effects of inflammatory cytokines on the basal ganglia (Goldsmith and Rapaport 2020; Perry et al. 2021). Fourth, metabolic syndrome has been associated with cognitive deficits in schizophrenia and may therefore play a role in motivation deficits (Hagi et al. 2021). Fifth, addictions have complex relationships with motivation. Tobacco and cannabis smoking and alcohol misuse are frequent in schizophrenia and may have a bilateral relationship with motivation deficits (Bahorik et al. 2017; Laksmidewi and Soejitno 2021; Schermitzler et al. 2021). Sixth, some antipsychotic treatments induce secondary negative symptoms including motivation deficits (Artaloytia et al. 2006; Mas et al. 2013; Kirkpatrick 2014; Fervaha et al. 2015). Seventh, childhood trauma may induce long-term motivation deficits (Kasparek et al. 2020).

In summary, the importance of motivation deficits in the functioning and quality of life of schizophrenia is now established, but its impact on risky health behaviours and the potential aetiological factors has not been determined in a comprehensive real-world sample.

Our aim was therefore to determine the impact of motivation deficits on risky health behaviour in addition to functioning and quality of life, and to determine the factors associated with motivation deficits in real-world schizophrenia. Our hypothesis was that motivation deficits were associated with increased overweight/obesity and/or metabolic syndrome, decreased physical activity level, more frequent addictive behaviour in addition to impaired functioning and quality of life. Among potential aetiological factors, we hypothesised that a positive association would be found between motivation deficits and depression, sleep disorders, antipsychotics side effects, childhood trauma and inflammation.

2. Population and methods

2.1. Study population

The FACE-SZ (FondaMental Academic Centres of Expertise for Schizophrenia) cohort is a national cohort created in 2010. The participants were consecutively recruited at a national level in 10 Schizophrenia Expert Centres (Bordeaux, Clermont-Ferrand, Colombes,

Créteil, Grenoble, Lyon, Marseille, Montpellier, Strasbourg, Versailles) (www.fondation-fondamental.org) (Schürhoff et al. 2018; Fond et al. 2020).

2.1.1. Inclusion criteria

The participants included in this cohort are clinically stabilised patients (defined by no hospitalisation and no treatment changes during the 8 weeks before evaluation) with a DSM-IV-TR diagnosis of schizophrenia (F20*) or schizoaffective disorder (F25*). Diagnosis was confirmed at inclusion by two trained psychiatrists of the Schizophrenia Expert Centres network. Diagnoses interviews were carried out by two independent psychiatrists according to the Structured Clinical Interview for Mental Disorders (SCID 1.0) (First MB, et al 2002) module B to H (Psychotic and associated symptoms, psychotic disorders, mood disorders, substance use disorders, anxiety disorders, somatoform disorders and eating disorders).

2.1.2. Exclusion criteria

All patients with other diagnoses than schizophrenia (except for comorbid major depression, anxiety disorder, eating disorder and addictions) and those not speaking French were excluded.

2.2. Collected data

All participants included in the FACE-SZ cohort receive a one-day long standardised battery of clinical assessments. The present participants received the 2015-updated battery. The details of psychometric properties and the rationale for the choice of the scales are described in a synthesis article (Schürhoff et al. 2015).

2.2.1. Motivation deficits definition and measurement

No specific scale has been developed so far to assess goal-directed motivation in schizophrenia patients, and motivation is not explored in the most frequently psychotic symptom scale for schizophrenia, the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) (Kay et al. 1987). We have therefore chosen the dimension of motivation evaluated in the lifestyle self-reported questionnaire battery, the Pittsburgh Sleep Questionnaire Index (Buysse et al. 1989). In this questionnaire, participants were asked the following question: 'In the past 30 days, how difficult was it for you to be sufficiently motivated to carry out your activities?'. They had four modalities: Not difficult at all – Somewhat difficult – Slightly difficult – Very difficult. The participants answering 'very difficult' were classified in the 'severe motivation deficits' group, the others in the control group.

2.2.2. Variables potentially explained by severe motivation deficits

The first set of variables included variables that were considered as potentially impacted by motivation, despite the cross-sectional design of the study. The purpose was therefore to determine if motivation may explain these variables.

2.2.2.1. Functioning. We explored daily functioning with the Global Assessment of Functioning scale (GAF) (Startup et al. 2002) and the Professional and Social Performance scale (PSP) (Morosini et al. 2000) (four subscores: socially useful activities, personal and social relationships, self-care and disturbing and aggressive behaviours).

2.2.2.2. Quality of life. Quality of life was assessed using the Schizophrenia – Quality of Life – 18 items (SQoL-18) questionnaire (eight dimensions: Self-Esteem, Sentimental Life, Familial relationships, Friendships, Autonomy, Psychological Well-being, Physical Well-being, Resilience, and a total Index score) (Auquier et al. 2003; Boyer et al. 2010) and EuroQol-5 Dimensions (EuroQol-5) questionnaire (with 6 subscores: mobility, autonomy, mobility, physical pain, anxiety/depression and self-reported global health status) (Mulhern et al. 2014).

Outcomes associated with health risky behaviour. We included body mass index, metabolic syndrome, physical activity, tobacco smoking, severe nicotine dependence (defined by a Fagerström questionnaire score $\geq$7) (Heatherton et al. 1991), and alcohol and cannabis use disorders and clinical global impression score (Haro et al. 2003) in this section. Physical activity level was assessed with the Global Physical Activity Questionnaire (Rivière et al. 2018).

2.2.3. Variables potentially explaining severe motivation deficits

2.2.3.1. Sociodemographic and early life variables. The present study has a cross-sectional design and no causal relationship can be inferred. However, retrospective/early life data was collected, including education level (a continuous variable, number of years of scholarship from primary school), childhood trauma questionnaire, age at schizophrenia onset, age at first antipsychotic treatment, age at first thymic episode, lifetime number of thymic episodes and lifetime history of suicide attempt. This data was reported by the

patient, her/his relatives (when present) and from the medical records sent by the treating psychiatrist to limit memorisation bias.

2.2.3.2. Current symptomatology. As psychiatric symptoms may influence motivation, psychotic symptomatology (PANSS total score and positive and negative factors) (continuous), current depressive episode (Calgary Depression rating Scale for Schizophrenia score $\geq$ 6) (Addington et al. 1993) (binary), current manic episode (Young Mania Rating Scale score $\geq$12) (binary), current sleep disorder (Pittsburgh Sleep Questionnaire Index sleep disorder subscore (Buysse et al. 1989) (binary), insight into illness (Birchwood total score and subscale scores: insight into illness, insight into symptoms and insight into the need for treatment) (continuous), current eating disorder defined with the Structured Clinical Interview for Mental Disorders (SCID 1.0) (First et al. 2002)) (binary).

2.2.3.3. Substance consumption and physical health. Alcohol and cannabis use disorders were defined with the Structured Clinical Interview for Mental Disorders (SCID 1.0) (First et al. 2002)) (binary), tobacco smoking status (binary) and coffee consumption (binary) were self-reported and the presence of at least one physical chronic disease (binary) was determined with the medical records yielded by the patients, her/his relatives and her/his treating physicians. Metabolic syndrome definition was detailed in a previous paper (Godin et al. 2015) in accordance with the World Health Organisation recommendations. Inflammation was proxied by the high sensitivity C-reactive protein (hs-CRP) blood level that was measured with an assay using nephelometry (Dade Behring). Hs-CRP blood level has been described a good proxy of central inflammation (Felger et al. 2018).

2.2.3.4. Treatments and treatment side effects. We included treatment variables (second generation antipsychotics, anticholinergic drugs, clozapine treatment, antidepressants, mood stabilisers, benzodiazepine (binary variables)). The antipsychotic treatments were classified according to their Anatomical-Therapeutic-Clinical ATC class. First-generation antipsychotics (FGA) were defined by ATC class N05AA to AC (phenothiazines), NO5AD (butyrophenones), NO5AF (thioxanthenes). Second-generation antipsychotics (SGA) were defined by ATC class N05AH (diazepines, oxazepines, thiazepines and oxepines) and NO5AL (benzamides) (Misdrahi et al. 2019). Treatment side-effects were assessed with the continuous scores of validated scales (extrapyramidal symptoms with the Simpson&Angus Scale (Simpson and Angus 1970), akathisia with the Barnes Akathisia Scale (BAS) (Barnes 1989), sexual dysfunctions with the self-reported Sexual Functioning Questionnaire (SFQ) (Smith et al. 2002)). Medication adherence was assessed with the Medication Adherence Rating Scale (MARS) (continuous) (Fond et al. 2017).

2.3. Statistical analysis

All variables were presented using measures of means and dispersion (standard deviation) for continuous data and frequency distribution for categorical variables. The data was examined for normal distribution with the Shapiro–Wilk test and for homogeneity of variance with the Levene test. Comparisons between patients with severe motivation deficits and those without using the chi-square test for categorical variables. Continuous variables were analysed with Student t-tests for normally distributed data and in case of normality violation, additional Mann-Whitney tests were performed to confirm the result. As detailed in the rationale, the present study was hypothesis-driven, no correction for multiple testing has been therefore carried out (Bender and Lange 2001).

The following set of data was included in the univariate analyses of the model 1 (Table 1) aiming at exploring which variables could be explained by severe motivation deficits: Global Assessment of Functioning scale score, Professional and Social Performance scale total score and subscores, SQoL-18 total Index score and eight dimensions scores (Self-Esteem, Sentimental Life, Familial relationships, Friendships, Autonomy, Psychological Well-being, Physical Well-being, Resilience), EQ5D total score and its 6 subscores, body mass index, metabolic syndrome, Global Physical Activity Questionnaire score, current tobacco smoking and severe nicotine dependence, current alcohol and cannabis use disorders, Clinical Global Impression score. In multivariate analyses, one model was carried out for each variable associated with severe motivation deficits with a p value $<$0.20 in univariate analyses (Global Assessment of Functioning scale score, Professional and Social Performance scale total score and subscores, SQoL-18 and EQ5D total scores and subscores, Global Physical Activity Questionnaire score, severe nicotine dependence, current alcohol disorder. Age and sex were forced in all models.

The following set of data was included in the univariate analyses of the model 2 (Table 2) aiming at

explaining severe motivation deficits (motivation was considered here as dependent variable): age, sex, education level, childhood trauma questionnaire score, age at schizophrenia onset, age at first antipsychotic treatment, age at first thymic episode, lifetime number of thymic episodes, lifetime history of suicide attempt, PANSS positive and negative factors, current depressive episode, current manic episode, insight into illness (Birchwood total score and subscale scores: insight into illness, insight into symptoms and insight into the need for treatment), current eating, alcohol, cannabis use disorders, tobacco smoking status, coffee consumption, body mass index, metabolic syndrome, hs-CRP blood level, second generation antipsychotics, anticholinergic drugs, clozapine treatment, antidepressants, mood stabilisers, benzodiazepine, extrapyramidal symptoms Simpson&Angus scale score, Barnes Akathisia Scale score, Sexual Functioning Questionnaire score, medication Adherence Rating Scale score. Severe nicotine dependence was not included as this variable is reported for smokers only.The variables associated with severe motivation deficits with a p value <0.20 in the univariate analyses were included in the multivariate model (age, lifetime history of suicide attempt, PANSS positive factor, current depressive episode, Birchwood total score, current alcohol disorder, second generation antipsychotics, current sleep disorder, Barnes Akathisia Scale score, Medication Adherence Rating Scale score). Sex was forced. Metabolic syndrome, alcohol, cannabis and tobacco were therefore included in both model 1 and model 2 (as we assumed a bilateral association based on literature review).

To understand more precisely the symptoms associated with motivation deficits, the associations between motivation deficits and each of the PANSS and CDSS symptoms were analysed (univariate analysis) (supplementary Table 1). Two subgroup analyses were carried out to understand the role of mood disorders: one after removing patients with schizoaffective disorders and one after removing patients with major depressive disorder.

2.4. Ethical considerations

The study was carried out in accordance with ethical principles for medical research involving humans (WMA, Declaration of Helsinki) and the French Jardé law. The assessment protocol was approved by the relevant ethical review board (CPP-Ile de France IX, 18th January 2010). All data was collected anonymously. As this study include data coming from regular care assessments, a non-opposition form was signed by all participants.

3. Results

Overall, 561 patients (416 (74.2%) men, 138 (24.6%) with schizo-affective disorders, 120 (21.4%) with major depressive disorder) were included in the FACE-SZ cohort between 1st January 2015 and 31th December 2019. Overall, 235 (41.9%) were included in the 'severe motivation deficits' group.

3.1. Variables potentially explaining severe motivation deficits (*Table 1*)

In multivariate analyses, individuals with severe motivation deficits were found to be older (adjusted odds ratio (aOR) 1.031, $p = 0.009$), to have more frequently history of suicide attempt (aOR = 2.297, $p = 0.001$), to have slightly higher positive symptoms (aOR = 1.052, $p = 0.006$), and insight into illness (aOR = 1.104, $p = 0.013$), to be more frequently diagnosed with current major depressive episode (aOR = 2.627, $p < 0.001$), to have more sleep disorders (aOR = 1.474, $p = 0.024$) and to have lower medication adherence (aOR = 0.836, $p = 0.001$) independently of gender, current alcohol use disorder, second-generation antipsychotics and akathisia. No significant association was found for negative symptoms, childhood trauma and inflammation. More specifically, motivation deficits were associated with the following psychotic and depressive symptoms (Table S1): delusions, hallucinations, persecution, passive social withdrawal, somatic concern, anxiety, guiltiness, depression, unusual thoughts, impulsivity, active social withdrawal, subjective depressive mood, hopelessness, pathological guiltiness, self-depreciation, morning depression and suicidal ideation.

3.2. Variables potentially explained by severe motivation deficits (*Table 2*)

Severe motivation deficits were found to be significantly associated with the following variables independently of age and sex: functioning (GAF score $B = -0.194$, $p < 0.001$, PSP total score: $B = -0.159$, $p < 0.001$ (socially useful activities subscore only)), quality of life (S-Qol-18 total index score ($B = -0.486$, $p < 0.001$) and sentimental life, self-esteem, friendships, autonomy, psychological and physical well-being, resilience subscores), EQ5D-5L total score ($B = -0.437$, $p < 0.001$) (and for all EQ5D-5L domains:

Table 1. Model 1: variables potentially explained by severe motivation deficits (independent variable) in stabilised outpatients with schizophrenia.

	Univariate model			Multivariate model[a]	
Variables	No motivation deficit or mild to moderate motivation deficits $N = 326$ (58.1%)	Severe motivation deficits $N = 235$ (41.9%)	p	aOR (95% IC) or standardised beta	Adjusted p value[a]
Functioning					
Global Assessment of Functioning score	**53.26 (14.65)**	**47.73 (12.80)**	**<0.001**	**−0.194**	**<0.001**
PSP impaired professional functioning subscore	**0.70 (0.46)**	**0.1 (0.39)**	**0.002**	**0.124**	**0.005**
PSP impaired social functioning subscore	0.73 (0.44)	0.78 (0.41)	Ns		
PSP self neglect subscore	0.19 (0.39)	0.26 (0.44)	0.068	0.067	ns
PSP increased aggressiveness subscore	0.05 (0.21)	0.07 (0.26)	Ns		
PSP total score	**56.2 (15.9)**	**52.2 (15.5)**	**<0.001**	**−0.159**	**<0.001**
Quality of life					
Sentimental life (S-QoL subscore)	**41.89 (29.47)**	**26.05 (28.10)**	**<0.001**	**−0.258**	**<0.001**
Self-esteem (S-QoL subscore)	**59.65 (24.32)**	**32.84 (27.63)**	**<0.001**	**−0.455**	**<0.001**
Familial relationships (S-QoL subscore)	72.67 (23.17)	67.79 (27.70)	0.002	−0.081	0.056
Friendships (S-QoL subscore)	**57.82 (25.62)**	**45.45 (29.20)**	**<0.001**	**−0.211**	**<0.001**
Autonomy (S-QoL subscore)	**65.26 (23.59)**	**50.65 (27.31)**	**<0.001**	**−0.274**	**<0.001**
Psychological well-being (S-QoL subscore)	**64.74 (24.24)**	**41.32 (22.92)**	**<0.001**	**−0.044**	**<0.001**
Physical well-being (S-QoL subscore)	**56.17 (23.53)**	**29.63 (22.88)**	**<0.001**	**−0.492**	**<0.001**
Resilience (S-QoL subscore)	**64.12 (24.29)**	**45.44 (27.51)**	**<0.001**	**−0.330**	**<0.001**
Quality of Life (S-QoL Index score)	**60.29 (15.56)**	**42.41 (15.62)**	**<0.001**	**−0.486**	**<0.001**
Mobility (EQ5D subscore)	**1.26 (0.65)**	**1.52 (0.82)**	**<0.001**	**0.164**	**<0.001**
Autonomy (EQ5D subscore)	**1.13 (0.44)**	**1.38 (0.73)**	**<0.001**	**0.205**	**<0.001**
Activity (EQ5D subscore)	**1.66 (0.88)**	**2.64 (1.02)**	**<0.001**	**0.459**	**<0.001**
Pain (EQ5D subscore)	**1.70 (0.93)**	**2.18 (1.15)**	**<0.001**	**0.210**	**<0.001**
Anxiety/depression (EQ5D subscore)	**2.12 (1.00)**	**3.10 (1.18)**	**<0.001**	**0.406**	**<0.001**
Self-reported global health level (EQ5D subscore)	**71.04 (17.3)**	**52.02 (20.22)**	**<0.001**	**−0.448**	**<0.001**
Quality of Life (EQ5D total score)	**0.76 (0.20)**	**0.54 (0.24)**	**<0.001**	**−0.437**	**<0.001**
Outcomes associated with health-risky behaviour					
Body Mass Index (kg/m2)	26.63 (5.50)	26.57 (5.66)	Ns		
Metabolic syndrome	73 (27.9%)	50 (25.6%)	Ns		
Physical activity level (GPAQ score)	94.28 (152.29)	67.43 (135.04)	0.086	−0.085	ns
Current alcohol use disorder	**17 (10.2%)**	**25 (19.8%)**	**0.021**	**2.141 (1.120–4.093)**	**0.021**
Current tobacco smoking	168 (53.0%)	117 (52.2%)	Ns		
Severe nicotine dependence (among smokers only)	**35 (21.1%)**	**51 (45.1%)**	**<0.001**	**2.906 (1.681–5.024)**	**<0.001**
Current cannabis use disorder	22 (10.6%)	18 (11.5%)	Ns		
Clinical global impression score	**3.94 (1.35)**	**4.36 (1.18)**	**<0.001**	**0.162**	**<0.001**

BPAQ: Buss-Perry Aggression Questionnaire; CGI: Clinical Global Impression scale; MARS: Medication Adherence Rating Scale; PSP Professional and Social Functioning scale; SQoL-18: self-reported quality of life scale for schizophrenia.

[a]Adjusted for age and sex. The presented multivariate model includes the verbal aggression subscore of the BPAQ. All BPAQ subscores were tested in separate multivariate models to avoid multicollinearity, with no change in the results (data not shown).

The variables associated with severe motivation deficits in multivariate analyses ($p < 0.05$) are in bold. Ns: non significant ($p > 0.05$). The p values of variables with statistical tendency (p value between 0.05 and 0.10) were fully written.

mobility, autonomy, activity, physical pain, anxiety-depression and perceived global health status), alcohol use disorder (aOR = 2.141, $p = 0.021$), severe nicotine dependence (aOR = 2.906, $p < 0.001$), clinical global impression score (standardised beta(B): 0.162, $p < 0.001$). No significant association was found for body mass index, metabolic syndrome or physical activity level.

In subgroup analyses, all associations were maintained statistically significant except for PSP socially useful activity, which was not significant after removing patients with schizoaffective disorders or those with major depressive disorders ($p > 0.050$). The association between severe motivation deficit and respectively alcohol use disorders and S-QoL family relationships subscore became statistically significant after removing patients with major depressive disorders (aOR = 3.100, $p = 0.018$ and $B = -0.106$, $p = 0.030$) but not those with schizoaffective disorders ($p > 0.050$).

4. Discussion

In 561 stabilised patients with schizophrenia living in the community, we found that more than 40% reported severe motivation deficits. These deficits were associated with impaired socially useful activities but not social functioning and self-neglect. They were associated with the impairment of almost all domains of psychological and physical quality of life, alcohol

Table 2. Model 2: variables potentially explaining severe motivation deficits (dependent variable) in stabilised outpatients with schizophrenia.

	Univariate model			Multivariate model[a]	
Variables	No motivation deficit or mild to moderate motivation deficits $N = 326$ (58.1%)	Severe motivation deficits $N = 235$ (41.9%)	p	aOR (95% IC)	adjusted p value[a]
Sociodemographic and early life variables, *N* or Mean (% or SD)					
Age (years)	**30.55 (8.39)**	**32.35 (9.80)**	**0.023**	**1.031 (1.008–1.055)**	**0.008**
Gender (male)	175 (74.5%)	242 (74.0%)	Ns	1.195 (0.738–1.934)	Ns
Education level (years)	12.25 (2.70)	12.50 (2.55)	Ns		
Childhood trauma Questionnaire total score	40.82 (10.98)	41.73 (11.48)	Ns		
Age at schizophrenia onset (years)	21.10 (5.81)	21.35 (7.03)	Ns		
Age at first antipsychotic treatment (years)	22.34 (5.9)	22.98 (6.79)	Ns		
Age at first thymic episode (years)	21.38 (6.43)	20.32 (6.78)	Ns		
Lifetime number of thymic episodes	2.59 (2.32)	2.71 (2.70)	Ns		
Lifetime history of suicide attempts	**44 (14.0%)**	**78 (34.4%)**	**<0.001**	**2.297 (1.413–3.733)**	**0.001**
Current symptomatology N or Mean (% or SD)					
Positive symptoms (PANSS subscore)	**13.22 (5.30)**	**15.37 (6.18)**	**<0.001**	**1.052 (1.014–1.090)**	**0.006**
Negative symptoms (PANSS subscore)	18.25 (7.07)	18.93 (6.75)	Ns		
Current depressive episode (CDSS score $\geq$ 6)	**35 (10.9%)**	**85 (37.4%)**	**<0.001**	**2.627 (1.586–4.349)**	**<0.001**
Current manic episode (YMRS score $\geq$ 12)	4 (1.3%)	4 (1.8%)	Ns		
Current sleep disorder	**82 (25.2%)**	**106 (45.1%)**	**<0.001**	**1.474 (1.051–2.066)**	**0.024**
Current eating disorder	17 (9.2%)	18 (11.8%)	Ns		
Insight (Birchwood total score)	**8.8 (3.0)**	**9.4 (2.7)**	**0.001**	**1.104 (1.021–1.194)**	**0.013**
Insight of symptoms (Birchwood subscore)	**2.94 (1.22)**	**3.18 (1.12)**	**0.020**		
Insight of illness (Birchwood subscore)	**2.55 (1.43)**	**3.06 (1.19)**	**<0.001**		
Insight of treatment need (Birchwood subscore)	3.17 (1.00)	3.26 (0.91)	Ns		
Substance consumption and physical health, N (%)					
Current alcohol use disorder	17 (10.2%)	25 (19.8%)	0.021	2.020(0.947–4.309)	0.069
Current tobacco smoking	168 (53%)	117 (52.2%)	Ns		
Current cannabis use disorder	22 (10.6%)	18 (11.5%)	Ns		
Coffee consumption	195 (73.6%)	132 (69.5%)	Ns		
Current chronic physical disease	52 (40.6%)	36 (3.7%)	Ns		
Body Mass Index (kg/m2)	26.63 (5.50)	26.57 (5.66)	Ns		
Metabolic syndrome	73 (27.9%)	50 (25.6%)	Ns		
Hs-CRP level (mg/L)	2.90 (5.42)	2.88 (4.73)	Ns		
Treatments and treatment side-effects, N or Mean (% or SD)					
Second Generation Antipsychotics	189 (80.4%)	243 (74.3%)	0.090	0.880 (0.536–1.446)	Ns
Anticholinergic drugs	49 (15.0%)	41 (17.4%)	Ns		
Clozapine	51 (15.6%)	39 (16.6%)	Ns		
Antidepressants	81 (28.8%)	80 (42.1%)	0.003	1.294 (0.814–2.056)[a]	Ns
Mood stabilisers	40 (12.3%)	37 (15.7%)	Ns		
Benzodiazepine	58 (17.8%)	53 (22.6%)	Ns		
Extrapyramidal side-effects (SAS score)	0.27 (0.37)	0.26 (0.35)	Ns		
Akathisia (BAS score)	0.37 (0.80)	0.59 (0.99)	0.006	1.207 (0.967–1.508)	0.096
Sexual functioning score (men)	8.05 (5.85)	7.96 (5.16)	Ns		
Sexual functioning score (women)	7.57 (5.58)	8.11 (5.99)	Ns		
Medication adherence (MARS score)	**6.81 (2.21)**	**5.72 (2.00)**	**<0.001**	**0.836 (0.753–0.928)**	**0.001**

BAS: Barnes Akathisia Scale; CDSS: Calgary Depression Scale for Schizophrenia; MARS: Medication Adherence Rating Scale; PANSS: Positive and Negative Syndrome Scale; SAS: Simpson–Angus Scale; YMRS: Young Mania Rating Scale.

[a]As severe motivation deficits is here the variable to explain, all variables associated with severe motivation deficits with a p value <0.2 were included in the multivariate model. Antidepressant were strongly associated with current major depressive episode and could not be entered in the multivariate model because of colinearity. The multivariate results presented for antidepressants were extracted from a subanalysis replacing current major depressive episode by antidepressants (other associations remained significant in this alternative model).

The variables associated with severe motivation deficits in multivariate analyses ($p < 0.05$) are in bold. Ns: non significant ($p > 0.05$). The p values of variables with statistical tendency (p value between 0.05 and 0.10) were fully written.

use disorder and nicotine dependence. We found no significant association of motivation deficits with body mass index, metabolic syndrome or physical activity level. In the second model, motivation deficits were strongly associated with major depression, history of suicide attempt, current sleep disorders and low medication adherence. While positive symptoms and insight were marginally associated with motivation deficits, we found no association with negative symptoms, inflammation, antipsychotics or antidepressants treatments.

Motivation deficits were associated with almost all psychological and physical domains of quality of life of the FACE-SZ participants, which confirms that motivation deficits are one of the major unmet needs in real-world schizophrenia. We have reproduced previous findings underlying the strong association between motivation deficits and objective impaired

functioning, especially socially useful activities (Ang et al. 2020). Unemployment is a major pejorative outcome of schizophrenia (Tsang et al. 2010) and motivation deficits should therefore be specifically targeted during rehabilitation interventions. It should be underlined that these deficits were not associated with impaired objective social functioning or self-neglect in our results. This is an additional argument to distinguish goal-directed motivation from social motivation (Uchino et al. 2021).

These results add evidence for the complex relationships between alcohol, tobacco and motivation deficits (Bahorik et al. 2017; DeAtley et al. 2020). While most of the tobacco studies in schizophrenia were focussed on motivation to quit smoking, we found that severe nicotine dependence was strongly associated with goal-orientated motivation deficits in schizophrenia smokers. We also found that motivation deficits were associated with alcohol use disorders, replicating the results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study (Bahorik et al. 2017). Motivation deficits should therefore be addressed in smoking cessation and alcohol reduction programs. On the contrary, the present results are not in favour of a role of motivation deficits in the success of weight loss or physical activity enhancement programs in schizophrenia.

The second model has yielded important directions for future motivation-enhancing programs.

First, the complex bilateral relationships between motivation and sleep, depression, suicide, and medication adherence has been explored outside schizophrenia but only in a one-to-one basis (Kenney et al. 2013; Russell et al. 2018; Liverant et al. 2021). The present study is the first to gather these factors that should be further explored in prospective follow-up studies and interventions. This model suggests that sleep, depression, suicide, medication adherence and positive symptoms play independent roles and that each of these factors should be targeted to address motivation deficits. The role of depression and sleep in motivation is well known outside schizophrenia. However, we found that our results were maintained in patients without major depressive disorders or schizoaffective disorders, confirming that mood do not explain all motivation deficit issues. The association between medication adherence and motivation deficits independently of the previous factors may be explained by decreased motivation to take medications or by the subjective negative side effects of the treatments (Misdrahi et al. 2016). While clozapine decreases positive symptoms and suicide (three factors associated with motivation deficits in our results), patients treated with clozapine were not found to have less motivation deficits than clozapine-free ones. Based on our results, no treatment seems to be associated with increased or decreased motivation deficits, even antidepressants that were previously suggested to be effective on negative symptoms (Rummel et al. 2006). Contrary to our expectations, we found no association of motivation deficits with the PANSS negative factor. More specifically, motivation deficits were only associated with social withdrawal. Our results are therefore in favour of the hypothesis that motivation deficits and negative symptoms are underpinned by different pathophysiological substrates and with different relations to outcomes and that depression and sleep better explain motivation deficits than negative symptoms (Kimhy et al. 2006; Galderisi et al. 2013).

These results should be taken with caveats as they are cross-sectional. However, they yield important clues to developed precision medicine-based motivation enhancing programs in schizophrenia. There is currently a major gap between the unmet need to address motivation deficits in schizophrenia in clinical practice (supported by our results) and the lack of research and guidelines in the field. There is no mention of motivation deficits in the last updates of the World Federation of Societies of Biological Psychiatry (WFSBP) and the National Institute for Health and Care Excellence (NICE) guidelines for schizophrenia (NICE clinical guideline 2014), even in the 'special circumstances' guidelines including depression, suicidality, substance use disorders, pregnancy and lactation (Hasan et al. 2015). We suggest that a specific chapter could be added in the next update. We carried out a pubmed research review with the search paradigm 'Schizophrenia AND (motivation or avolition)' (28th May 2021). Among pharmacological approaches, roluperidone (Strauss et al. 2019; Harvey et al. 2020), rasagiline (Buchanan et al. 2015), minocycline (Kelly et al. 2015; Krynicki et al. 2021) and oxytocin (Bradley et al. 2020) have been explored in small sample size randomised trials with no clinical applications in daily practice so far. Among other interventions, motivational interview, behavioural activation, smartphone intervention, incentives and informationally administered rewards and neurostimulation have shown promising but still preliminary results (Prikryl et al. 2013; Hager et al. 2015; Schlosser et al. 2018; Hunt et al. 2019; Luther et al. 2020; Bodén et al. 2021; Brandt et al. 2021). In our sample, motivation decreases with age, suggesting that clinicians should implement

interventions (regardless of their type) early in the illness course to prevent motivation deficits.

4.1. Strengths

This study is the first study to include such a wide range of clinical and treatment factors to explore motivation deficits in schizophrenia. All patients were evaluated with a standardised battery. The national area of recruitment of 10 centres limited the selection bias. All evaluators were trained in the FondaMental Schizophrenia Expert Network, with regular training sessions (at least once a year) for the clinicians-rated scales (Fond et al. 2020). Our depression and functioning evaluations were objective/clinician-rated evaluations. It is therefore unlikely that depressive symptoms may have influenced the patients' perception of their own functioning contrary to previous works leading to artefactual associations. We have chosen the most severe level of motivation deficits to define the motivation deficits group. Despite this stringent threshold, we identified more than 40% of the patients reporting severe motivation deficits.

4.2. Limits

These results are cross-sectional and no causal relationship can be inferred. The next step will be to explore the impact of motivation deficits on illness trajectory during follow-up. Our results push for the need of an adequate dedicated scale to evaluate motivation in schizophrenia, distinguishing goal-directed activities from social activities. We found no significant associations of physical activity with motivation deficits in our analyses. However preliminary data suggests that aerobic exercise may increase motivation in schizophrenia (Shimada et al. 2019) and accurate physical activity assessment is complex with discrepancies between objective and subjective measurements. We also found no argument for inflammation to play a role in motivation deficits in stabilised treated outpatients. We used only hs-CRP as inflammatory marker. Other markers like IL-6 may be more relevant to explore this association (Al-Hakeim et al. 2015), but it is not available in daily clinical practice. The association of depression, suicide and motivation deficits suggests also a potential role of self-stigma that has not been captured in the FACE-SZ database and should be investigated.

5. Conclusion

Motivation deficits are frequent and remain persistent unmet need in real-world schizophrenia that should be addressed in future guidelines. Based on our results, literature and clinical experience, we recommend to address in priority major depression, sleep, suicide, positive symptoms (when present and as early as possible) and medication adherence to improve motivation deficits of schizophrenia.

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Author contributions

LB performed the statistical analysis. TK, LB and GF wrote the first complete manuscript. All authors were involved in the patients' recruitment, the clinical evaluation, acquisition of the clinical data, modified the manuscript and approved the final version.

Statement of interest

None to declare.

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Chapitre 3 : Prévalence et impact des dysfonctions sexuelles dans les troubles schizophréniques débutants

A- Définition de la santé sexuelle et des dysfonctions sexuelles

B- Lien entre dysfonctions sexuelles et troubles schizophréniques

C- Sexual Dysfunction in Schizophrenia - A Systematic Review and Meta-Analysis (JAMA psychiatry)

A- Définition de la santé sexuelle et des dysfonctions sexuelles

La santé sexuelle, selon l'Organisation Mondiale de la Santé (OMS), est un état de bien-être physique, émotionnel, mental et social en relation avec la sexualité. Elle ne se limite pas à l'absence de maladie, de dysfonction ou d'infirmité. La santé sexuelle nécessite une approche positive et respectueuse de la sexualité et des relations sexuelles, ainsi que la possibilité d'avoir des expériences sexuelles qui sont sources de plaisir et exemptes de toute contrainte, discrimination et violence. Pour l'OMS, la santé sexuelle fait partie intégrante de la santé globale de l'individu et de son bien-être(99).

L'intégration de la santé sexuelle dans la santé globale est fondamentale, car elle influence et est influencée par de nombreux autres aspects de la santé(100). Les problèmes de santé sexuelle peuvent avoir des répercussions significatives sur la santé mentale, comme l'anxiété, la dépression, et sur la santé physique, à travers des maladies sexuellement transmissibles ou des problèmes de fertilité, par exemple. Inversement, la santé générale peut affecter la santé sexuelle ; des conditions telles que le diabète, les maladies cardiaques et les pathologies mentales que nous allons développer, peuvent impacter la fonction sexuelle. Ainsi, une approche globale de la santé qui inclut la santé sexuelle est cruciale pour le bien-être général des individus, soulignant l'importance d'une éducation sexuelle complète, de l'accès aux soins de santé sexuelle et reproductive et de la lutte contre les stigmates et discriminations liés à la sexualité(101).

La santé sexuelle, souvent considérée comme un aspect privé et intime de l'existence humaine, joue pourtant un rôle crucial dans la **qualité de vie globale**. La sexualité est une source fondamentale de plaisir et de satisfaction personnelle, contribuant à l'épanouissement émotionnel et physique. Elle permet non seulement d'explorer et d'exprimer l'intimité, mais aussi de renforcer le lien affectif entre partenaires. Ces expériences positives sont essentielles pour le bien-être mental, car elles favorisent l'estime de soi, la confiance en soi et la satisfaction globale dans la vie(102).

La sexualité a un **impact significatif sur la santé physique**. Des relations sexuelles saines et consenties peuvent avoir des effets bénéfiques, tels que la réduction du stress, l'amélioration de la qualité du sommeil, et même la diminution de la douleur. Les activités sexuelles peuvent également contribuer à maintenir un système cardiovasculaire sain, soulignant ainsi le lien direct entre la santé sexuelle et la santé physique en général(103).

La santé sexuelle est **étroitement liée à la santé mentale(104)**. Les dysfonctions ou insatisfactions dans la sphère sexuelle peuvent entraîner stress, anxiété, et dépression. À l'inverse, une vie sexuelle épanouie peut améliorer la résilience face au stress et augmenter le sentiment général de bien-

être. La capacité à exprimer et à vivre sa sexualité sans honte ni culpabilité est donc un aspect essentiel de la santé mentale et du développement personnel.

Quatrièmement, la sexualité joue un rôle central dans la **construction de l'identité personnelle et sociale**. La façon dont les individus perçoivent leur propre sexualité, ainsi que la manière dont ils choisissent de l'exprimer, sont intrinsèquement liées à leur sens de l'identité. Pour de nombreuses personnes, être capable d'exprimer librement leur sexualité, y compris l'orientation sexuelle et l'identité de genre, est essentiel pour se sentir validé et accepté au sein de la société. Cela contribue à un sentiment d'appartenance et à la construction de relations sociales significatives.

Enfin, la sphère sexuelle est un domaine important de la **communication et de l'intimité** dans les relations de couple, affectant profondément la qualité et la stabilité de ces relations. La capacité à communiquer ses désirs, ses besoins, et ses limites, ainsi que la capacité à écouter et à respecter ceux de son partenaire, sont fondamentales pour une relation saine et épanouie. L'intimité sexuelle peut renforcer le lien émotionnel entre les partenaires, favorisant ainsi une relation durable et satisfaisante.

En somme, la santé sexuelle est un aspect fondamental de la qualité de vie, influençant le bien-être physique, émotionnel, et social. Son intégration et son expression saines sont cruciales pour l'épanouissement individuel et relationnel.

B- Lien entre dysfonctions sexuelles et troubles schizophréniques

La prise en compte de la santé sexuelle en psychiatrie, et plus spécifiquement dans le cadre des troubles schizophréniques débutants, revêt une importance cruciale bien que trop **souvent négligée(105)**.
Dans les troubles schizophréniques, particulièrement aux stades initiaux, les individus peuvent expérimenter des modifications significatives de leur fonctionnement psychosocial, y compris dans leur vie sexuelle.

Les dysfonctions sexuelles, fréquemment rapportées chez les personnes souffrant de troubles schizophréniques, en particulier dans les phases initiales de la maladie, ont un **impact négatif sur la motivation et l'engagement(41)**.
Dans le contexte des troubles schizophréniques débutants, ces dysfonctions peuvent être exacerbées par les symptômes psychotiques eux-mêmes, tels que les délires et les hallucinations, ainsi que par les effets secondaires des médicaments antipsychotiques.
Par ailleurs, le traitement des troubles schizophréniques implique souvent l'utilisation de médicaments antipsychotiques, qui peuvent eux-mêmes contribuer aux dysfonctions sexuellesvia une hyper prolactinémie(106). Cette interaction médicamenteuse peut créer un cercle vicieux où la personne se sent moins motivée à suivre son traitement en raison des effets secondaires. Cela peut aggraver les symptômes de la maladie et diminuer davantage l'envie de participer à la vie sociale ou à d'autres aspects de la vie quotidienne. La reconnaissance et le traitement de ces dysfonctions sexuelles (107) dans les premiers épisodes psychotiques sont donc cruciaux pour améliorer la qualité de vie et la motivation des personnes affectées.

Ensuite, et comme nous l'avons vu dans le chapitre précédent, les personnes souffrant de troubles schizophréniques peuvent connaître une perte de motivation, qui affecte leur capacité à initier et à maintenir des activités dans plusieurs domaines de la vie, y compris ceux liés à la sexualité. Cette apathie peut réduire l'intérêt ou le désir d'engager des interactions sexuelles, ce qui a un impact non seulement sur leur satisfaction personnelle mais également sur les relations de couple. **La reconnaissance et l'adressage des questions de santé sexuelle** peuvent donc jouer un rôle crucial dans l'amélioration de la motivation et dans la facilitation de l'engagement dans un traitement global, en aidant les patients à retrouver un sens de normalité et à améliorer leur interaction sociale.

De plus, aborder la santé sexuelle dans le traitement des troubles schizophréniques permet de reconnaître et de traiter les effets secondaires des médicaments antipsychotiques, qui peuvent inclure la dysfonction érectile, la diminution de la libido, ou d'autres troubles sexuels. En discutant ouvertement

de ces préoccupations, les psychiatres peuvent ajuster les traitements pour minimiser ces effets secondaires, **améliorant ainsi la qualité de vie des patients** et leur adhérence au traitement.

La prise en compte de la santé sexuelle offre également une opportunité de renforcer la communication et la compréhension entre les patients et les professionnels de la santé, permettant une prise en charge plus intégrative des troubles schizophréniques. En intégrant cette dimension dans le plan de soin, on favorise une approche plus personnalisée et empathique, qui tient compte de tous les aspects de la vie du patient, et pas seulement des symptômes psychotiques.
Les conclusions d'une publication réalisée au préalable dans notre service (41) indiquaient que la prise en charge des symptômes dépressifs pourrait constituer une stratégie clé pour améliorer les effets indésirables sexuels chez les personnes souffrantes de troubles schizophréniques.

C- **Sexual Dysfunction in Schizophrenia - A Systematic Review and Meta-Analysis,** publié dans JAMA psychiatry

Nous avons donc réalisé la première méta analyse existante concernant les effets indésirables sexuels dans les troubles schizophréniques.

Notre étude, une méta-analyse et revue systématique approfondie de 72 études impliquant 21 076 participants atteints de troubles schizophréniques, a exploré la prévalence de la dysfonction sexuelle et les facteurs associés à l'hétérogénéité des dysfonctions au sein de cette population. Elle met en lumière une prévalence élevée et une grande variabilité des dysfonctions sexuelles, soulignant ainsi un aspect souvent négligé mais crucial de la prise en charge des troubles schizophréniques.
Cette recherche a utilisé des sources de données variées sans restriction linguistiques ou temporelles, reflétant un effort exhaustif pour capturer la totalité de la littérature existante sur le sujet.

Notre démarche répond à un manque notable dans la littérature scientifique, où les données précises et consolidées sur les dysfonctions sexuelles associées aux troubles schizophréniques sont rares. En fournissant des statistiques fiables et globales, cette méta-analyse offre une base solide pour évaluer l'ampleur du problème, permettant ainsi aux professionnels de santé de reconnaître l'importance de la santé sexuelle dans le cadre global de la maladie.

Les résultats révèlent une **prévalence globale de dysfonctions sexuelles de 56,4%**, avec des spécificités selon le genre : 55,7% chez les hommes et 60% chez les femmes. Les dysfonctions les plus fréquentes identifiées étaient la dysfonction érectile chez les hommes et la perte de libido, tandis que chez les femmes, l'aménorrhée et la dysfonction orgasmique étaient prédominantes. Ces chiffres mettent en exergue l'importance de la santé sexuelle dans la les troubles schizophréniques, affectant significativement les deux sexes.

L'étude a également identifié plusieurs facteurs contribuant à l'hétérogénéité des dysfonctions sexuelles, incluant le design de l'étude, la localisation géographique, les données sociodémographiques, l'usage d'alcool, le diagnostic psychiatrique, la sévérité de la maladie, ainsi que l'utilisation d'antidépresseurs et d'anxiolytiques.

Notre analyse a mis en évidence des associations entre l'utilisation de médicaments antidépresseurs et une prévalence moindre de dysfonction sexuelle, ce qui rejoint notre première publication(41). Cette observation suggère que le traitement de la dépression comorbide pourrait être une stratégie efficace pour améliorer la santé sexuelle chez les individus atteints de troubles

schizophréniques, soulignant **l'interconnexion entre la santé mentale et la santé sexuelle.**

Le constat que la dysfonction sexuelle reste élevée chez les personnes atteintes de troubles schizophréniques, sans amélioration notable au fil du temps ni avec l'utilisation des antipsychotiques de seconde génération, appelle à une réévaluation des approches thérapeutiques actuelles. Cela souligne la nécessité d'intégrer des stratégies de prise en charge de la santé sexuelle dans le traitement global des troubles schizophréniques.

Les données obtenues grâce à cette méta-analyse soulignent la nécessité d'intégrer la santé sexuelle dans l'évaluation et le traitement des troubles schizophréniques dès leurs débuts. Reconnaître les dysfonctions sexuelles comme une composante fréquente des troubles schizophréniques permet aux cliniciens d'adopter une approche plus holistique. Cela prend en compte non seulement les symptômes psychiatriques mais aussi les aspects psychosociaux et somatiques de la maladie. De plus, cela encourage l'élaboration de stratégies de traitement personnalisées, qui visent à améliorer la qualité de vie globale des patients, y compris leur bien-être sexuel.
Une telle approche peut également favoriser une meilleure adhérence au traitement et une meilleure alliance thérapeutique.

Les résultats de cette méta-analyse ont des implications importantes pour la recherche future et les politiques de santé publique. Ils mettent en évidence le besoin urgent de développer des interventions spécifiques et des programmes de soutien axés sur la santé sexuelle des personnes atteintes de troubles schizophréniques. Cela peut stimuler la recherche de solutions innovantes, telles que de nouvelles modalités de traitement ou des approches thérapeutiques complémentaires, qui abordent à la fois les symptômes des troubles schizophréniques et ses effets sur la santé sexuelle.

En conclusion, notre méta-analyse met en évidence la prévalence élevée de dysfonctions sexuelles chez les individus atteints de troubles schizophréniques et la complexité des facteurs associés. Elle appelle à une prise de conscience et à une prise en charge plus holistique de la santé sexuelle dans le cadre des troubles schizophréniques, proposant des pistes de traitement innovantes et soulignant l'importance de traiter les troubles comorbides tels que la dépression pour améliorer la qualité de vie des patients.

JAMA Psychiatry | Original Investigation

Sexual Dysfunction in Schizophrenia
A Systematic Review and Meta-Analysis

Théo Korchia, MD; Vincent Achour, MD; Mélanie Faugere, PhD; Ali Albeash, MsC; Dong Keon Yon, MD, PhD; Laurent Boyer, MD, PhD; Guillaume Fond, MD, PhD

IMPORTANCE In individuals with schizophrenia, antipsychotic-induced dysfunctions are frequent but often underexplored in clinical practice.

OBJECTIVE To synthetize the data of observational studies exploring the prevalence of sexual dysfunction in individuals with schizophrenia-spectrum disorders as well as associated factors.

DATA SOURCES A systematic literature search without language or time restrictions was conducted in Google, Google Scholar, PubMed/MEDLINE, Science Direct, and Université Sorbonne Paris Cité for studies published up to June 8, 2022.

STUDY SELECTION All observational studies reporting a prevalence of sexual dysfunction in schizophrenia-spectrum disorder were included.

DATA EXTRACTION AND SYNTHESIS The MOOSE guidelines with independent extraction by 2 observers and random-effects models were used.

MAIN OUTCOMES AND MEASURES The prevalence of sexual dysfunction and each specific dysfunction.

RESULTS A total of 72 of 1119 studies from 33 countries on 6 continents published from inception to June 2022 were included with a total of 21 076 participants with schizophrenia. The pooled global prevalence of sexual dysfunctions was 56.4% (95% CI, 50.5-62.2), with a prevalence of 55.7% (95% CI, 48.1-63.1) for men and 60.0% (95% CI, 48.0-70.8) for women. The most frequent sexual dysfunction was erectile dysfunction in men (44%; 95% CI, 33.5-55.2), followed by loss of libido in men (41%; 95% CI, 30.7-51.4), ejaculation dysfunction in men (39%; 95% CI, 26.8-51.8), orgasm dysfunction in women (28%; 95% CI, 18.4-40.2), and amenorrhea in women (25%; 95% CI, 17.3-35.0). Factors associated with heterogeneity were study design, time and location, sociodemographic data, alcohol use disorder, psychiatric diagnosis, illness severity, and the use of antidepressants and anxiolytics. Sexual dysfunctions were more frequent in schizophrenia vs schizoaffective disorders, and erectile disorders were less frequent in individuals with longer illness duration. Antidepressant and mood stabilizer prescriptions were associated with lower rates of erection disorders (β, −6.30; 95% CI, −10.82 to −1.78); $P = .006$ and −13.21; 95% CI, −17.59 to −8.83; $P < .001$, respectively) and ejaculation disorders (β, −6.10; 95% CI, −10.68 to −1.53; $P = .009$ and β, −11.57; 95% CI, −16.34 to −6.80; $P < .001$, respectively). No obvious improvements in the rates of sexual dysfunction at other times were found, and there were conflicting results regarding antipsychotic classes.

CONCLUSIONS AND RELEVANCE This systematic review and meta-analysis found a high prevalence of sexual dysfunction among individuals with schizophrenia, with considerable heterogeneity in associated factors. The findings also suggest that some dysfunctions may be explained by schizophrenia. The association between lower rates of dysfunction and antidepressant use suggests that treating comorbid depression could be an effective strategy to improve sexual health. A lack of data on metabolic parameters and physical health in general was also noted, while these issues are frequent in the care of schizophrenia.

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Supplemental content

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The attention given to sexual health in schizophrenia has increased since the end of the 20th century.[1] However, schizophrenia has been associated with increased sexual dysfunction only in a small meta-analysis[2] of 10 observational studies (3 case-control studies and 7 cross-sectional studies) published in 2020. An meta-analysis[3] of sexual dysfunction in psychiatric patients taking antipsychotics and limited to studies with sexual dysfunction as the primary objective and using validated scales concluded that antipsychotics were a major source of heterogeneity in the prevalence of sexual dysfunction in schizophrenia, with quetiapine, ziprasidone, perphenazine, aripiprazole, olanzapine, risperidone, haloperidol, clozapine, and thioridazine having an increasing impact on sexual function ranging from 16% (quetiapine) to 60% (thioridazine). One of the major pathophysiological mechanisms is probably the inhibition of dopamine D2 receptors. This inhibition in the tuberoinfundibular pathway is associated with increased serum prolactin levels.[4] A dose of more than 200 ng/mL of risperidone[5] induces amenorrhea, breast tenderness, and galactorrhea in women and hypogonadism in men by disrupting the secretion of GnRH by the hypothalamus.[6,7] Antipsychotic-induced sexual dysfunctions may also occur independently of increased prolactinemia due to increased antiparkinsonian adverse effects, including blunted affect and anhedonia.[4] Anti-α1-adrenergic receptor inhibition may also induce sexual dysfunctions through relaxation of the intracavernosal smooth muscle fibers, inducing erection and ejaculation dysfunctions in men.[8] Anti-H1 receptor inhibition induces sedation, which may alter satisfactory sexual activity.[4]

Antipsychotic-induced sexual dysfunctions thus appear to be heterogeneous by their type and pathophysiological mechanism. Distinguishing each specific sexual dysfunction may increase the accuracy of interventions. A recent systematic review[9] found that the most frequent disorders in schizophrenia were loss of libido and erectile dysfunction in men. Decreased libido may be the result of the negative syndrome of the illness associated with anhedonia and social withdrawal.[10] Major depression is a frequent comorbidity of schizophrenia found in approximately one-third of patients.[11] It is underscreened and undertreated due to confusion with the negative symptoms of schizophrenia.[11] Several potential risk factors for sexual dysfunction in schizophrenia have been identified, including comorbid major depression, unemployment, singlehood, tobacco smoking, and cannabis and alcohol use disorders.[9] In summary, we need to update the data on sexual dysfunction prevalence, as the only meta-analysis on this topic was published more than 10 years ago, and we need a quantitative analysis of associated factors that may explain the heterogeneity of sexual dysfunctions in schizophrenia with a focus on each sexual dysfunction (in each and both sexes) resulting from different pathophysiological mechanisms. The objectives of the present study were to determine the prevalence of sexual dysfunction in schizophrenia and of each specific dysfunction (sexual dysfunctions in each sex, loss of libido, orgasm dysfunction, genital pain, erectile and ejaculation dysfunctions, amenorrhea, and galactorrhea) and to identify factors associated with heterogeneity.

Key Points

Question What is the prevalence of sexual dysfunction in individuals with schizophrenia and the factors associated with heterogeneity of dysfunction?

Findings In this systematic review and meta-analysis of 72 studies including 21 076 participants with schizophrenia, prevalence and heterogeneity of global sexual dysfunction were high. Study design, time and location, sociodemographic data, alcohol use disorder, psychiatric diagnosis, illness severity, and the use of antidepressants and anxiolytics were associated with heterogeneity; associations were also found between lower prevalence of sexual dysfunction and use of antidepressant medication.

Meaning The findings in this study suggest that prevalence of sexual dysfunction remains high in people with schizophrenia with no obvious improvement over time or better tolerance of second-generation antipsychotics; treating depression may be a key point to reduce sexual dysfunction in individuals with schizophrenia.

Methods

Search Strategy and Sources of Information

The study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline.[12] We performed a literature review on 5 digital databases: PubMed/MEDLINE, Science Direct, Google Scholar, Google, and Université Sorbonne Paris Cité from inception to June 8, 2022. The search paradigm is presented in eAppendix 1 in Supplement 1. The protocol was registered in PROSPERO (CRD42022355766). Ethical approval was not sought or required, as the study involved no individual patient data.

Eligibility Criteria

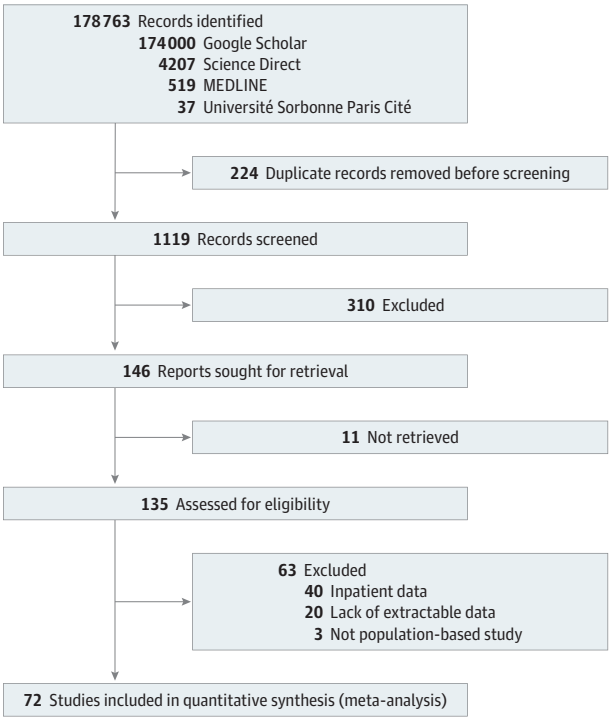
All observational studies reporting a prevalence of sexual dysfunction (by any tool of measure, which includes nonvalidated tools, such as binary questions and unstructured clinical interviews) in patients with schizophrenia or schizoaffective disorder were included in the present work. In the case of longitudinal studies, cross-sectional baseline data were included. While English search words were used for PubMed/MEDLINE, Science Direct, Google Scholar, Google and French words for Université Sorbonne Paris Cité, there was no language limitation to ensure the comprehensiveness of the data, and the articles were translated as needed to extract relevant data.

All interventional studies were excluded to eliminate a participation bias and because randomized clinical trials overselect participants.[13] Studies including inpatients were excluded, assuming that the stress of the hospitalization and the short-term phase of the disease would have a major impact on sexual dysfunction. Studies assessing only treatment-resistant patients were not included, as we hypothesized an overestimation bias in these patients, who usually receive high

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Figure 1. PRISMA Flow Diagram



Flow diagram for new systematic reviews, which included searches of databases and registers only.

doses of treatments with persistent psychotic symptomatology. In summary, the aim of the present work was to assess sexual dysfunction in the daily life of treated patients, not in resistant or hospitalized patients.

Data Extraction

Two investigators (M.F. and V.A.) independently performed the literature review and extracted data. Controversial articles were discussed in a meeting between the 2 investigators, and in case of persistent disagreement, a third investigator (G.F.) was consulted and made the final decision. The extracted data are presented in eAppendix 2 in Supplement 1.

Assessment of Methodological Quality

The study quality assessment was carried out independently by 2 investigators (M.F. and V.A.) using the modified version of the Newcastle-Ottawa Scale (NOS).[14] Studies were scored from 0 (poor quality) to 10 points (excellent quality). Studies scoring 7 or more points were considered good quality studies.

Statistical Analysis

A random logistic regression model was used to calculate the pooled prevalence estimates of sexual dysfunction and its 95% CI.[15] A sensitivity analysis was performed with the inverse-variance random-effects model, confirming the robustness of the findings. Heterogeneity between studies was quantified using the I^2 statistic.[16] Sensitivity analyses were performed using the leave-one-out method. Publication bias was assessed graphically with a funnel plot and statistically with the Thompson-Sharp test when the number of studies exceeded 10.[17] Subgroup analyses for binary variables and univariate meta-regressions for quantitative variables were used to assess factors moderating the pooled prevalence estimate of sexual dysfunction from individual studies. All analyses were performed using the meta package in R version 4.1.3 (R Foundation).[18]

Results

Study Characteristics

Seventy-two studies published between 1979 and 2021 were included in the random-effects model.[6,7,19-88] The flow diagram is presented in **Figure 1**. Among those, 35 studies included data on the prevalence of orgasm dysfunction, 34 on loss of libido, 10 on genital pain, 33 on erectile dysfunction, 19 on ejaculation dysfunction, 6 on amenorrhea, and 5 on galactorrhea. The 63 excluded studies and the reason for exclusion are presented in eAppendix 3 in Supplement 1.

The selected articles included 21 076 patients from 33 countries on 6 continents. The study characteristics are reported in eAppendices 4-6 in Supplement 1. The study quality assessment is presented in eAppendix 7 in Supplement 1. Overall, 30 studies (41.7%) were classified in the good quality group. A total of 59 studies (81.9%) used a standardized questionnaire to assess sexual dysfunctions (eAppendices 4-6 in Supplement 1). The most frequent sexual dysfunction scales were the Arizona Sexual Experience scale[89] (N = 19), Changes in Sexual Functioning Questionnaire[90] (N = 7), Sexual Functioning Questionnaire[91] (N = 6), Female Sexual Function Index[92] (N = 6), Udvalg for Kliniske Undersogelser[93] (N = 4), and Psychotropic-Related Sexual Dysfunction Questionnaire[94] (N = 4). Thirteen studies (18.1%) used a clinical semistructured interview, 6 (8.3%) used an original questionnaire, and 1 (1.4%) used medical records.

Pooled Prevalence Estimate of Global Sexual Dysfunctions

The pooled prevalence estimates of global sexual dysfunctions and sexual dysfunctions in men and women with schizophrenia are presented in **Figure 2**. The pooled estimates and their 95% CIs were as follows: global prevalence of sexual dysfunctions, 56.4% (95% CI, 50.5-62.2), with values ranging from 3% to 98%; loss of libido, 40.6% (95% CI, 30.7-51.4); orgasm dysfunction, 28.0% (95% CI, 18.4-40.2); and genital pain, 6.1% (95% CI, 2.8-12.7). There was significant heterogeneity within the results for global dysfunction and sexual dysfunctions (I^2 for men, 98% [$P < .001$]; I^2 for women, 96% [$P < .01$]). The forest plots are presented in **Figure 3** and eAppendices 8-10 in Supplement 1.

Pooled Prevalence Estimates of Sexual Dysfunctions in Men With Schizophrenia

The pooled estimates and their 95% CIs were as follows: male sexual dysfunction, 55.7% (95% CI, 48.1-63.1); erectile dysfunction, 44.0% (95% CI, 33.5-55.2); and ejaculation

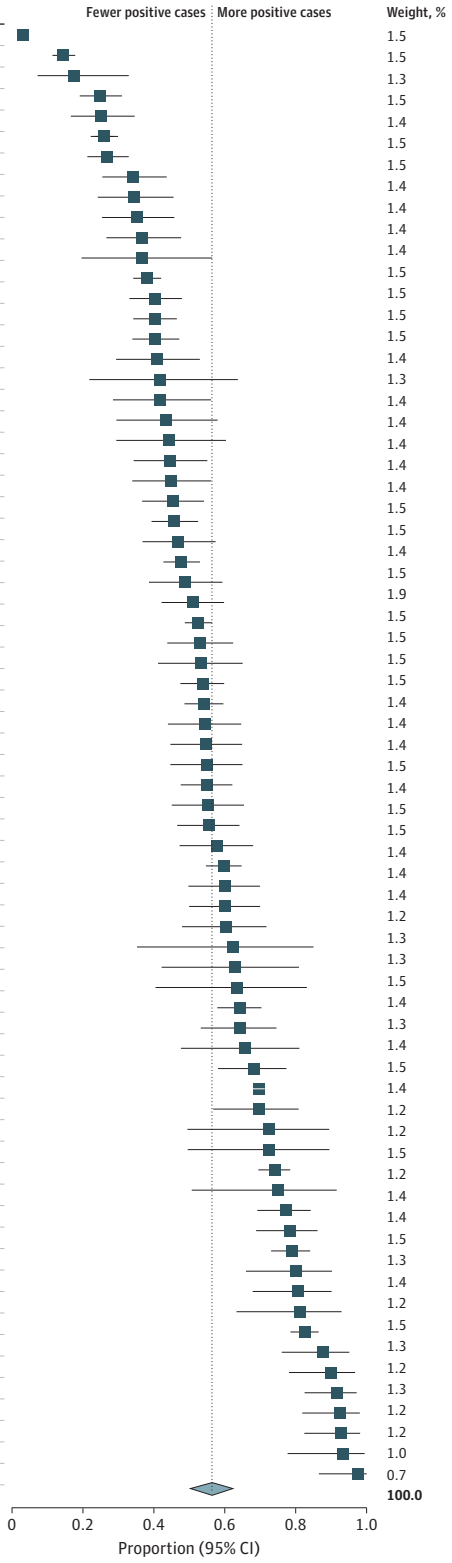
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Figure 2. Studies Exploring the Prevalence of Sexual Dysfunctions in Schizophrenia (Random-Effects Model)

Study	Events	Total	Proportion (95% CI)	Weight, %
Xiang et al,[49] 2011	178	5874	0.03 (0.03-0.04)	1.5
Bitter,[29] 2005	83	571	0.15 (0.12-0.18)	1.5
Istikoglou et al,[43] 2009	7	40	0.17 (0.01-0.33)	1.3
Warden,[23] 1997	57	230	0.25 (0.19-0.31)	1.5
Nebhinani et al,[52] 2012	25	100	0.25 (0.17-0.35)	1.4
Millier et al,[59] 2014	314	1206	0.26 (0.24-0.29)	1.5
Hashimoto et al,[51] 2012	68	252	0.27 (0.22-0.33)	1.5
Bhat,[56] 2013	41	120	0.34 (0.26-0.43)	1.4
Hariri et al,[41] 2009	29	84	0.35 (0.24-0.46)	1.4
Khan et al,[70] 2017	32	91	0.35 (0.25-0.46)	1.4
Esan and Esan,[73] 2020	33	90	0.37 (0.27-0.47)	1.4
Bobes et al,[26] 2003	241	632	0.38 (0.34-0.42)	1.5
Yasui-Furukori et al,[50] 2012	77	191	0.40 (0.33-0.48)	1.5
Oyekanmi et al,[53] 2019	111	275	0.40 (0.35-0.46)	1.5
Fond et al,[78] 2019	96	237	0.41 (0.34-0.47)	1.5
Aggarwal et al,[77] 2019	31	76	0.41 (0.30-0.53)	1.4
Pairin,[60] 2015	10	24	0.42 (0.22-0.63)	1.3
Ghadirian et al,[7] 1982	23	55	0.42 (0.29-0.56)	1.4
Bhui et al,[22] 1997	23	53	0.43 (0.30-0.58)	1.4
Fortier et al,[27] 2003	20	45	0.44 (0.30-0.60)	1.4
Smith et al,[25] 2002	45	101	0.45 (0.35-0.55)	1.4
Kirino,[71] 2017	39	87	0.45 (0.34-0.56)	1.4
Olfson et al,[28] 2005	63	139	0.45 (0.37-0.54)	1.5
Montejo et al,[47] 2010	112	244	0.46 (0.40-0.52)	1.5
Zhang et al,[48] 2011	47	100	0.47 (0.37-0.57)	1.4
Kassew et al,[81] 2019	188	393	0.48 (0.43-0.53)	1.5
Kockott and Pfeiffer,[21] 1996	49	100	0.49 (0.39-0.59)	1.9
Nunes et al,[40] 2009	70	137	0.51 (0.42-0.60)	1.5
Oçok et al,[34] 2007	435	827	0.53 (0.49-0.56)	1.5
Wang et al,[65] 2016	67	126	0.53 (0.44-0.62)	1.5
Fujii et al,[44] 2010	191	352	0.54 (0.49-0.60)	1.5
Hocaoglu et al,[57] 2014	55	101	0.54 (0.44-0.64)	1.4
Shakir et al,[54] 2013	57	104	0.55 (0.45-0.65)	1.4
Nakhli et al,[58] 2014	55	100	0.55 (0.45-0.65)	1.4
Doane et al,[82] 2020	110	200	0.55 (0.48-0.62)	1.5
Yusufi et al,[35] 2007	57	103	0.55 (0.45-0.65	1.4
Sibinovic et al,[39] 2009	76	137	0.55 (0.47-0.64)	1.5
Liu-Seifert et al,[38] 2009	240	402	0.60 (0.55-0.65)	1.5
Castaño et al,[37] 2008	60	100	0.60 (0.50-0.70)	1.4
Howes et al,[33] 2007	62	103	0.60 (0.50-0.70)	1.4
Sathish Kumar and Sinha,[6] 2015	44	73	0.60 (0.48-0.72)	1.4
Lukoff et al,[20] 1986	10	16	0.62 (0.35-0.85)	1.2
Arató et al,[19] 1979	17	27	0.63 (0.42-0.81)	1.3
Romero Guillena,[68] 2016	14	22	0.64 (0.41-0.84)	1.3
Olisah et al,[61] 2016	164	255	0.64 (0.58-0.70)	1.5
Fan et al,[32] 2007	56	87	0.64 (0.53-0.74)	1.4
Bellnier,[66] 2016	23	35	0.66 (0.48-0.81)	1.3
Shetageri et al,[67] 2016	69	101	0.68 (0.58-0.77)	1.4
Dossenbach et al,[31] 2006	2665	3828	0.70 (0.68-0.71)	1.5
Simiyon et al,[64] 2016	44	63	0.70 (0.57-0.81)	1.4
Plevin et al,[36] 2007	16	22	0.73 (0.50-0.89)	1.2
Redman et al,[86] 2021	16	22	0.73 (0.50-0.89)	1.2
Huang et al,[79] 2019	310	418	0.74 (0.70-0.78)	1.5
Abdelatti et al,[83] 2020	15	20	0.75 (0.51-0.91)	1.2
Harley et al,[45] 2010	106	137	0.77 (0.69-0.84)	1.4
Rowel et al,[76] 2018	80	102	0.78 (0.69-0.86)	1.4
Hou et al,[62] 2016	195	247	0.79 (0.73-0.84)	1.5
Khawaja et al,[30] 2005	40	50	0.80 (0.66-0.90)	1.3
Martín et al,[74] 2018	46	57	0.81 (0.68-0.90)	1.4
Halouani et al,[69] 2017	26	32	0.81 (0.64-0.93)	1.2
Fanta et al,[75] 2018	349	422	0.83 (0.79-0.86)	1.5
Kumar et al,[87] 2021	50	57	0.88 (0.76-0.95)	1.3
Abdelatti et al,[83] 2018	45	50	0.90 (0.78-0.97)	1.2
Nagaraj et al,[42] 2009	66	72	0.92 (0.83-0.97)	1.3
Mullen et al,[24] 2001	50	54	0.93 (0.82-0.98)	1.2
Kokoszka et al,[46] 2009	52	56	0.93 (0.83-0.98)	1.2
Ben Mahmoud et al,[55] 2013	28	30	0.93 (0.78-0.99)	1.0
Gaber et al,[84] 2020	39	40	0.97 (0.87-1.00)	0.7
Random-effects model			**0.56 (0.50-0.62)**	**100.0**

Heterogeneity: $I^2 = 98\%$; $\tau^2 = .99$; $P < .001$

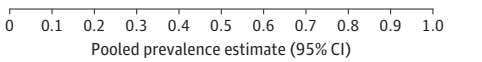


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Figure 3. Pooled Prevalence Estimates of the Specific Dysfunctions (Random-Effects Model)

Dysfunction	Pooled prevalence estimate (95% CI)	I^2, %
Genital pain (men and women)	6.1 (2.8-12.7)	89
Galactorrhea	7.7 (3.7-15.3)	77
Amenorrhea	25.1 (17.3-35.0)	86
Orgasm dysfunction (men and women)	28.0 (18.4-40.2)	97
Ejaculation disorder	38.6 (26.8-51.8)	97
Loss of libido (men and women)	40.6 (30.7-51.4)	96
Erection disorder	44.0 (33.5-55.2)	94



dysfunction, 38.6% (95% CI, 26.8-51.8). The forest plots are presented in Figure 3, **Figure 4**, and eAppendices 11-12 in Supplement 1.

Pooled Prevalence Estimates of Sexual Dysfunctions in Women With Schizophrenia

The pooled estimates and their 95% CIs were as follows: female sexual dysfunction, 60.0% (95% CI, 48.0-70.8); amenorrhea, 25.1% (95% CI, 17.3-35.0); and galactorrhea, 7.7% (95% CI, 3.7-15.3). The forest plots are presented in Figure 3, **Figure 5**, and eAppendices 13-14 in Supplement 1.

Leave-One-Out Analyses and Publication Bias

The leave-one-out analyses are presented in eAppendices 15-17 in Supplement 1. No study had a disproportionate effect on the pooled prevalence estimate of sexual dysfunction or on heterogeneity. The funnel plots are presented in eAppendices 18-20 in Supplement 1. Visual inspection of the forest plots did not identify substantial asymmetrical shape. The Thompson-Sharp test *P* values were significant for global sexual dysfunctions (t, 5.63; $P < .001$), sexual dysfunctions among men (t, 4.58; $P < .001$), sexual dysfunctions among women (t, 2.25; $P = .03$), orgasm dysfunction (t, −3.85; $P < .001$), and ejaculation disorder (t, −2.33; $P = .03$). The results were not significant for libido dysfunction or erection disorder.

Subgroup and Meta-Regression Analyses

Subgroup and meta-regression analyses are presented in eAppendices 21-23 (global dysfunctions) and 27-29 (specific dysfunctions) in Supplement 1, and meta-regression analyses are in eAppendices 24-26 (global dysfunctions) and 30-32 (specific dysfunctions) in Supplement 1. The significant associations are summarized as follows:

Study Design, Time, and Location

Compared to cohort studies, cross-sectional studies reported significantly higher rates of sexual, orgasm, and male sexual dysfunctions. Studies including consecutive participants reported significantly lower rates of loss of libido, male sexual dysfunction, and erectile dysfunction. Studies including sexual dysfunctions in their primary objective reported significantly higher rates of sexual dysfunctions. Studies including a validated tool for diagnosis reported higher rates of loss of libido. Studies including patient-reported diagnoses reported significantly higher rates of genital pain. Studies including clinical interview diagnosis reported lower rates of loss of libido and orgasm dysfunction. Studies including a clinician-rated tool diagnosis reported significantly higher rates of loss of libido. No significant association was found with study quality. We found that time and location were associated with higher rates of sexual dysfunction in more recent studies and lower rates in North America and Europe compared to the rest of the world.

Sociodemographic Variables

Lower rates of loss of libido were reported in studies including a higher proportion of men. Higher rates of genital pain were reported in studies including more male and single participants, and higher rates of loss of libido were reported in studies including more unemployed participants.

Physical Health and Addictions

There was a significant association between the percentage of patients with alcohol use disorders and lower rates of male sexual dysfunction. No other significant associations were found.

Psychiatric Diagnosis and Illness Severity

Globally, we found that higher loss of libido, orgasm dysfunction, and erection disorder were reported in studies including more patients with schizophrenia vs schizoaffective disorder. The rate of erectile dysfunction decreased with the mean duration of illness. Higher rates of female sexual dysfunction were significantly associated with positive scores on the Positive and Negative Syndrome Scale.

Antipsychotic Classes and Daily Dose (Chlorpromazine Equivalents)

We found contradictory results concerning antipsychotic classes (first generation vs second generation) and sexual dysfunctions, and it was not possible to identify a class or specific antipsychotic associated with a higher or lower prevalence of sexual dysfunction. Sexual dysfunction prevalence was mostly not reported according to the administered antipsychotic, and there were not enough studies to determine the sexual dysfunction prevalence in samples treated with homogenous antipsychotic treatment.

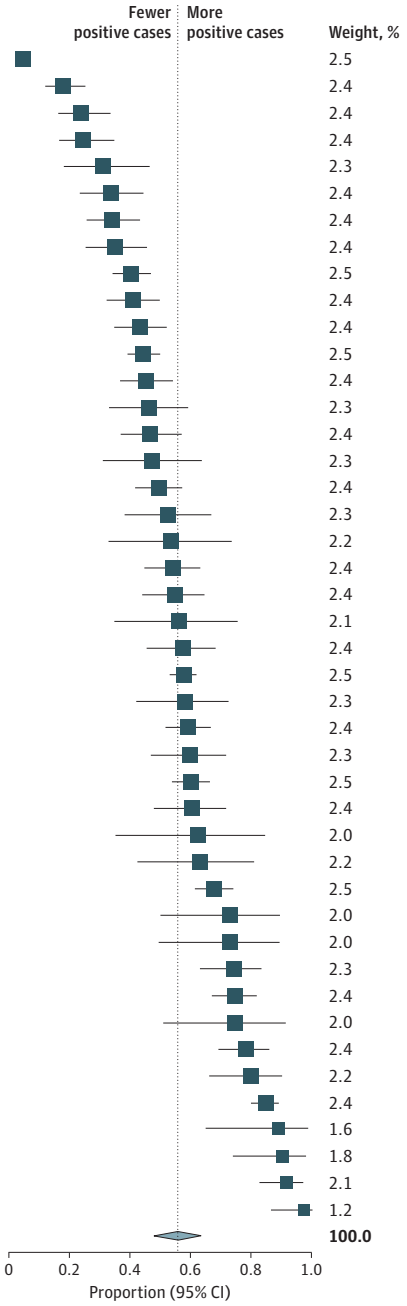
Other Psychotropic Drugs

Given that these were observational studies, patients were often administered multiple treatments other than antipsy-

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Figure 4. Studies Exploring the Prevalence of Sexual Dysfunctions in Men With Schizophrenia (Random-Effects Model)



Study	Events	Total	Proportion (95% CI)	Weight, %
Xiang et al,[49] 2011	158	3426	0.05 (0.04-0.05)	2.5
Warden,[23] 1997	27	149	0.18 (0.12-0.25)	2.4
Yasui-Furukori et al,[50] 2012	26	108	0.24 (0.16-0.33)	2.4
Nebhinani et al,[52] 2012	25	100	0.25 (0.17-0.35)	2.4
Esan and Esan,[73] 2018	14	45	0.31 (0.18-0.47)	2.3
Nunes et al,[40] 2009	28	84	0.33 (0.23-0.44)	2.4
Bhat,[56] 2013	41	120	0.34 (0.26-0.43)	2.4
Khan et al,[70] 2017	32	91	0.35 (0.25-0.46)	2.4
Oyekanmi et al,[53] 2012	111	275	0.40 (0.35-0.46)	2.5
Wu et al,[88] 2021	54	132	0.41 (0.32-0.50)	2.4
Fond et al,[78] 2019	63	145	0.43 (0.35-0.52)	2.4
Bobes et al,[26] 2003	173	389	0.44 (0.39-0.50)	2.5
Olfson et al,[28] 2005	63	139	0.45 (0.37-0.54)	2.4
Hocaoglu et al,[57] 2014	29	63	0.46 (0.33-0.59)	2.3
Zhang et al,[48] 2011	47	100	0.47 (0.37-0.57)	2.4
Bhui et al,[22] 1997	19	40	0.47 (0.32-0.64)	2.3
Montejo et al,[47] 2010	86	173	0.50 (0.42-0.57)	2.4
Howes et al,[33] 2007	28	53	0.53 (0.39-0.67)	2.3
Ghadirian et al,[7] 1982	14	26	0.54 (0.33-0.73)	2.2
Olisah et al,[61] 2016	66	122	0.54 (0.45-0.63)	2.4
Shakir et al,[54] 2013	57	104	0.55 (0.45-0.65)	2.4
Fortier et al,[27] 2003	14	25	0.56 (0.35-0.76)	2.1
Souaiby et al,[80] 2020	47	82	0.57 (0.46-0.68)	2.4
Uçok et al,[34] 2007	315	547	0.58 (0.53-0.62)	2.5
Suresh et al,[63] 2016	26	45	0.58 (0.42-0.72)	2.3
Fujii et al,[44] 2010	105	177	0.59 (0.52-0.67)	2.4
Fan et al,[32] 2007	39	65	0.60 (0.47-0.72)	2.3
Liu-Seifert et al,[38] 2009	153	255	0.60 (0.54-0.66)	2.5
Sathish Kumar and Sinha,[6] 2015	44	73	0.60 (0.48-0.72)	2.4
Lukoff et al,[20] 1986	10	16	0.62 (0.35-0.85)	2.0
Arató et al,[19] 1979	17	27	0.63 (0.42-0.81)	2.2
Huang et al,[79] 2019	158	233	0.68 (0.61-0.74)	2.5
Plevin et al,[36] 2007	16	22	0.73 (0.50-0.89)	2.0
Redman et al,[86] 2021	16	22	0.73 (0.50-0.89)	2.0
Harley et al,[45] 2010	60	81	0.74 (0.63-0.83)	2.3
Hou et al,[62] 2016	116	155	0.75 (0.67-0.81)	2.4
Abdelatti et al,[83] 2020	15	20	0.75 (0.51-0.91)	2.0
Rowel et al,[76] 2018	80	102	0.78 (0.69-0.86)	2.4
Khawaja et al,[30] 2005	40	50	0.80 (0.66-0.90)	2.2
Fanta et al,[75] 2018	246	290	0.85 (0.80-0.89)	2.4
Mullen et al,[24] 2001	16	18	0.89 (0.65-0.99)	1.6
Kokoszka et al,[46] 2009	28	31	0.90 (0.74-0.98)	1.8
Nagaraj et al,[42] 2009	66	72	0.92 (0.83-0.97)	2.1
Gaber et al,[84] 2020	39	40	0.97 (0.87-1.00)	1.2
Random-effects model			**0.56 (0.48-0.63)**	**100.0**

Heterogeneity: I^2 = 98%; τ^2 = .97; P < .001

chotics. Compared to other studies, erectile and ejaculation dysfunctions and loss of libido were significantly lower in studies including participants treated with antidepressants, and erectile and ejaculation dysfunctions decreased with the percentage of patients treated with antidepressants and mood stabilizers. Sexual dysfunctions in general among men and erectile and ejaculation dysfunctions were significantly lower in studies including patients with anxiolytics. Antidepressant and mood stabilizer prescriptions were associated with lower rates of erection disorders (β, −6.30; 95% CI, −10.82 to −1.78); P = .006 and −13.21; 95% CI, −17.59 to −8.83; P < .001, respectively) and ejaculation disorders (β, −6.10; 95% CI, −10.68 to −1.53; P = .009 and β, −11.57; 95% CI, −16.34 to −6.80; P < .001, respectively).

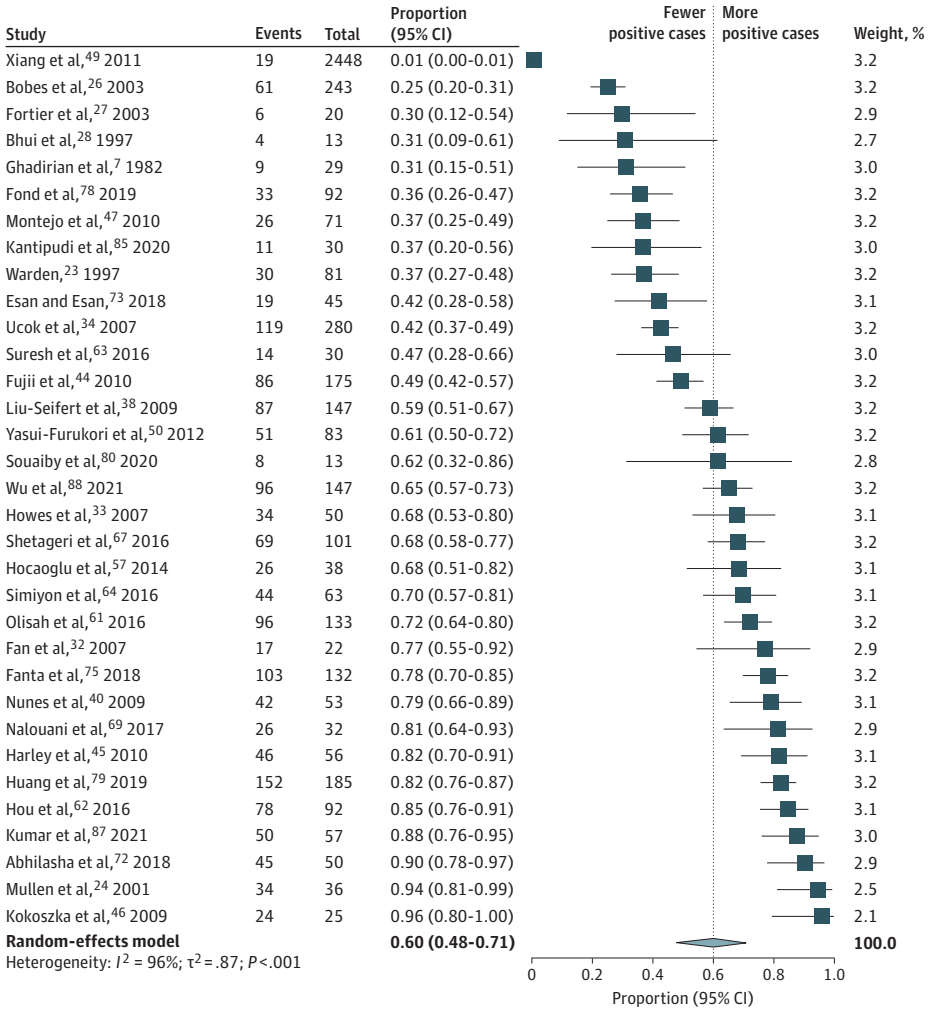
Comparative Pooled Prevalence Estimates of Sexual Dysfunction of the Inverse Variance Method vs Random Intercept Logistic Regression Model

The comparative pooled prevalence estimates of sexual dysfunction and 95% CIs for the inverse variance method vs ran-

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Figure 5. Studies Exploring the Prevalence of Sexual Dysfunctions in Women With Schizophrenia (Random-Effects Model)



dom intercept logistic regression model are presented in eAppendix 33 in Supplement 1.

Discussion

This systematic review and meta-analysis synthesized a high number of observational studies including quantitative data on the prevalence of sexual dysfunctions in schizophrenia published over 4 decades and 6 continents. The prevalence of sexual dysfunction in schizophrenia was found to be high and heterogeneous. Our results provided important data on the prevalence of each sexual dysfunction. The most frequent sexual dysfunction was erectile dysfunction (44% of men), followed by loss of libido (41%), ejaculation dysfunction (39% of men), orgasm dysfunction (28%), and amenorrhea (25% of women). Galactorrhea and genital pain were less explored and less frequent.

These rates are extremely high. For comparison, erectile dysfunction affects an estimated 30 million men in the US according to the National Institute of Diabetes and Digestive and Kidney Diseases.[95] The prevalence of erectile dysfunction increases with age, with approximately 12% of men younger than 60 years experiencing erectile dysfunction compared to 30% of men aged 70 years and older.[95] The prevalence of loss of libido, also known as hypoactive sexual desire disorder, is estimated to be approximately 10% in women and 5% in men in the US according to the American Psychiatric Association's *DSM-5*.[10]

We found multiple factors associated with this heterogeneity beyond the expected association with antipsychotics. Among these factors, study design (recruitment and tools but not quality) are classical factors inducing heterogeneity in prevalence studies. As expected, studies including sexual dysfunction in their primary objective reported a higher prevalence of sexual dysfunction. This may be explained by a selection bias.[96,97] Our results suggest that studies including nonconsecutive participants may have included a selection bias overestimating the findings. Cross-sectional studies reported higher rates than cohort studies. Except for population-

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based studies (which were not available for sexual dysfunctions), cohort studies may induce a selection bias at inclusion. For clinical trials, patients to be included in a follow-up cohort may not be representative of all real-life patients, with better compliance, lower addictions, and other clinical setting-related factors explaining lower sexual dysfunctions in cohort studies. Similar to other comorbidities of schizophrenia,[11] we found that some sexual dysfunctions were more frequently reported when a validated tool and a self-reported tool were used (compared to clinical interviews or nonvalidated tools). This may be particularly true if some patients are reluctant to answer or ashamed of answering questions about intimate areas during a clinical interview, which may also be modulated by age, sex of the patient, sex of the clinician, and cultural factors. The use of a self-reported validated tool could be actively promoted to improve screening in daily practice. This could be automated with online Patient-Reported Outcomes Measures (PROMs).[98] We found that the Arizona Sexual Experience scale was the most frequently used questionnaire in the studies included in this work that could be used as a PROM in clinical practice. Importantly, we found that limiting the results to high-quality studies did not change our results, which reinforces their robustness and the confidence we can have in them.

We found significant associations between the prevalence of sexual dysfunctions and time and location. We found that most sexual dysfunctions had a higher prevalence in recent studies than in ancient studies and no evidence of an improvement in sexual dysfunction prevalence with the release of second-generation antipsychotics. Time and location may also intersect with other factors, such as study design, as discussed above. Geographical discrepancies could also be explained by differences in prescription habits and general social and health factors (including prevention, lifestyle and health care systems). Of note, we found no significant difference in sexual dysfunction prevalence in schizophrenia between high-income countries and low- to middle-income countries, but data in Africa and Polynesia were limited.

Our purpose was to provide a picture of observational studies of real-world stabilized outpatients with schizophrenia. Stabilization does not mean remission, and we found that 3 studies including patients with higher psychotic symptomatology and higher positive and negative symptoms also reported more frequent orgasm dysfunction and loss of libido. However, these few data call for additional studies including participants with high positive or negative symptom levels to confirm these associations. It is probably impossible to discriminate the part of the mental illness itself in the onset of sexual dysfunctions. For example, we found that a lower prevalence of sexual dysfunction was reported in studies including more patients with schizoaffective disorders. We do not know if the results found for antidepressants are explained by an indication bias. A strikingly missing clinical factor is comorbid major depressive disorder. The association of major depressive disorder with sexual dysfunction has been robustly demonstrated in other psychiatric populations and in the general population.[99,100] A meta-analysis[11] of observational studies recently concluded that approximately one-third of individuals with stabilized schizophrenia are identified with comorbid major depressive disorder, that is, 3 to 4 times the prevalence of the general population. We found that the studies with the highest proportion of antidepressant, mood stabilizer, and anxiolytic prescriptions also reported lower rates of sexual dysfunctions compared to other studies, which is a compelling reason to investigate the role of major depression in the high prevalence of sexual dysfunctions in schizophrenia and their treatment. Thus, the systematic coscreening of sexual dysfunctions combined with major depression may be an effective strategy to improve the care of schizophrenia.

Limitations

This study has limitations. More than 80% of the included studies used validated tools, and their absence was only associated with a higher prevalence of loss of libido. Most factors known to increase sexual dysfunction in the general population (eg, hypertension, diabetes, overweight and obesity, tobacco smoking, and sleep disorders) were not identified as risk factors in our results; however, they were poorly explored in the included studies. Tobacco smoking and overweight or obesity are 2 major sources of sexual dysfunctions that are frequently present in people with schizophrenia, and their role should be better delimited. It is currently impossible to capture diet parameters, as no questionnaire has been specifically designed for this purpose. This issue will probably be addressed in the coming years.[101] These results may not be extrapolated to some continents, such as Africa and Polynesia, which were underrepresented. Additionally, the presence of publication bias in our meta-analysis cannot be entirely ruled out, as indicated by the statistical significance of the Thompson-Sharp test. However, the absence of a clear asymmetrical pattern in the funnel plots suggests that the likelihood of publication bias is relatively low. Heterogeneity or methodological differences may also contribute to the observed results.[17]

Conclusions

Four decades of studies have reported sexual dysfunction as extremely frequent in schizophrenia. Beyond methodological discrepancies partially explaining heterogeneity, we found important evidence in observational studies suggesting that improving the screening and treatment of depression may be an effective strategy to improve sexual health in patients with schizophrenia. Promoting systematic health assessment in sexual dysfunction studies could also help better understand associations between sexual dysfunction and metabolic parameters.

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Author Contributions: Drs Fond and Boyer had full access to all the data in the study and take responsibility for the integrity of the data and the

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accuracy of the data analysis. Drs Korchia, Archour, and Fond contributed equally.
Concept and design: Boyer.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Achour, Albeash, Yon, Boyer.
Critical review of the manuscript for important intellectual content: Korchia, Faugere, Boyer, Fond.
Statistical analysis: Albeash, Boyer, Fond.
Supervision: Yon, Boyer.

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Chapitre 4 : Comment accompagner le souhait de diminuer le traitement antipsychotique dans les troubles schizophréniques débutants

A- Nécessité du traitement antipsychotique dans les premiers épisodes psychotiques

B- Une compliance thérapeutique à discuter entre psychiatre et patient ?

C- **Collaborative discontinuation of antipsychotics after the first episode of psychosis**

A- Nécessité du traitement antipsychotique dans les premiers épisodes psychotiques

La prise en charge thérapeutique des troubles schizophréniques, notamment dans ses phases initiales, représente un enjeu majeur pour les professionnels de la santé. Le traitement antipsychotique précoce et continu parait essentiel, car il joue un rôle capital non seulement dans la maîtrise des symptômes aigus mais aussi dans la prévention des rechutes.

Dans le cadre des premiers épisodes psychotiques, l'intervention rapide avec des antipsychotiques peut réduire significativement la sévérité et la durée des épisodes psychotiques. Les directives cliniques recommandent de maintenir le traitement pendant au moins deux ans après un premier épisode psychotique et de prolonger cette période à cinq ans en cas de rechute(s), afin de stabiliser les symptômes et de réduire le risque de récidive.

Cependant, la gestion à long terme des troubles schizophréniques avec des antipsychotiques est souvent rendue complexe par la survenue d'effets secondaires, qui peuvent varier en intensité et en nature. Ces effets, notamment la prise de poids, la sédation, et les troubles métaboliques ou les effets indésirables sexuels (cf chapitre 3), représentent des obstacles significatifs à l'adhésion au traitement. La crainte et l'expérience de ces effets indésirables peuvent conduire certains patients à interrompre prématurément leur médication, compromettant ainsi leur rétablissement.

Parmi les effets secondaires, les dysfonctionnements sexuels constituent un problème particulièrement sensible et perturbant pour les patients. La diminution de la libido, les dysfonctionnements érectiles chez les hommes, et les troubles de l'orgasme chez les femmes, peuvent avoir des répercussions profondes sur les relations intimes et l'estime de soi. L'impact de ces effets sur la qualité de vie souligne l'importance d'aborder ouvertement ces préoccupations avec les patients, afin de trouver des solutions adaptées qui permettent de maintenir le traitement tout en minimisant ses inconvénients.

B- Une compliance thérapeutique à discuter entre psychiatre et patient ?

L'arrêt des traitements antipsychotiques est une question complexe et souvent négligée dans le parcours de soin des patients souffrant de troubles psychotiques, en particulier ceux qui vivent un premier épisode psychotique. Cette problématique revêt une importance cruciale, car la discontinuation du traitement peut entraîner des risques significatifs, notamment une augmentation du risque de rechute ou des syndromes de sevrage lors des arrêts brutaux. Les patients, après un premier épisode psychotique, peuvent exprimer le désir d'arrêter leur traitement pour diverses raisons, telles que les effets secondaires, le sentiment d'une amélioration de leur état ou le désir de gérer leur condition sans médication. Toutefois, cette décision doit être accompagnée, car les antipsychotiques jouent un rôle central dans la stabilisation de la condition du patient et la prévention des rechutes.

Face à cette problématique, il est essentiel d'adopter une **approche personnalisée et collaborative** dans la prise en charge des patients. Les professionnels de santé doivent écouter attentivement les préoccupations et les souhaits des patients concernant leur traitement, en pesant soigneusement les avantages de la continuation du traitement contre les risques associés à son arrêt. La prise en compte du point de vue du patient souffrant de troubles schizophréniques dans la poursuite du traitement antipsychotique est fondamentale pour plusieurs raisons, notamment en termes de motivation, de diminution des effets indésirables et de consolidation de l'alliance thérapeutique. Cette approche centrée sur le patient permet non seulement d'améliorer l'adhésion au traitement mais aussi de favoriser un rétablissement plus global et durable. La construction d'une relation de soin basée sur l'écoute et le respect mutuel est cruciale dans le traitement des troubles schizophréniques, une pathologie complexe caractérisée par des symptômes psychotiques tels que des hallucinations, des délires, et des troubles du comportement.
Une évaluation rigoureuse du risque de rechute, une éducation thérapeutique sur l'importance de la médication et un suivi étroit sont indispensables pour accompagner le patient dans cette démarche. En outre, l'implication des patients dans la prise de décision concernant leur traitement peut améliorer leur adhésion à celui-ci et, par conséquent, contribuer à un meilleur pronostic à long terme. La question de l'arrêt des traitements antipsychotiques souligne l'importance d'une prise en charge holistique et personnalisée des troubles psychotiques, qui tient compte non seulement des aspects médicaux mais aussi des préférences et du bien-être global du patient.

C- **Collaborative discontinuation of antipsychotics after the first episode of psychosis,** publié dans The Journal of Psychiatry & Neuroscience

Notre article publié dans le "Journal of Psychiatry and Neuroscience" (JPN) explore une question clinique fondamentale concernant l'arrêt encadré des traitements antipsychotiques chez les patients en début de psychose. Il s'agit d'une publication qui a été exposée au congrès mondial sur les troubles schizophréniques en 2023 à Toronto. Ce travail s'intéresse particulièrement aux dilemmes rencontrés par les cliniciens quant à la durée appropriée du traitement après un premier épisode psychotique et la façon de gérer les risques de rechute lors d'un arrêt du traitement.

Dans l'article, nous avons utilisé un cas clinique pour illustrer les défis et les considérations impliqués dans la prise de décision autour de la continuation ou de l'interruption des antipsychotiques. Le patient, un jeune adulte dont les études universitaires ont été interrompues en raison d'une hospitalisation psychiatrique pour un premier épisode de psychose, a d'abord été traité avec succès par la rispéridone, mais a arrêté le médicament à cause d'une prise de poids significative, un effet secondaire fréquent mais gênant (75).

En dépit des preuves soutenant l'usage continu des antipsychotiques pour réduire le risque de rechute(108), notre patient a décidé d'interrompre son traitement par aripiprazole en raison de la fatigue ressentie. Cette décision soulève le problème de la balance entre les bénéfices à long terme du traitement et les effets secondaires qui affectent la qualité de vie au quotidien (109).

Notre approche dans cet article a été d'offrir un cadre pour guider les cliniciens à travers le processus complexe d'interruption du traitement. Nous avons discuté de l'importance de la surveillance étroite, de la planification de la réduction progressive des médicaments et du maintien d'un contact régulier avec le gestionnaire de cas infirmier pour minimiser les risques de rechute (110).

Nous avons également mis en lumière la nécessité d'une alliance thérapeutique solide pour soutenir le patient durant cette période de transition. La recherche indique qu'une bonne relation thérapeutique, un environnement social favorable et l'absence de troubles concomitants tels que l'abus de substances augmentent les chances de succès lors d'un arrêt du traitement (111).

Cependant, nous reconnaissons dans notre travail que la question de savoir quand et comment arrêter le traitement reste sans réponse définitive. Les lignes directrices existantes ne fournissent pas de protocole clair, et la pratique clinique doit souvent être ajustée en fonction des caractéristiques individuelles du patient et de l'évolution de sa maladie(112).

Notre article ne se contente pas de présenter les données existantes, mais propose également une réflexion sur la manière dont les cliniciens peuvent aborder la question de l'arrêt du traitement avec leurs patients, en reconnaissant la légitimité de leurs préoccupations concernant les effets secondaires et leur désir de normalité(45).

Pour conclure, le travail que nous avons effectué souligne l'importance d'une approche personnalisée et centrée sur le patient dans le traitement de la psychose, en particulier pendant les phases initiales de la maladie.

The information in this column is not intended as a definitive treatment strategy but as a suggested approach for clinicians treating patients with similar histories. Individual cases may vary and should be evaluated carefully before treatment is provided. The patient described in this column is a composite with characteristics of several real patients.

Collaborative discontinuation of antipsychotics after the first episode of psychosis

Theo Korchia, MD; Hani Abdelhafez, MD, PhD; Alice Bretelle, MD; Ridha Joober, MD, PhD; Lena Palaniyappan, MD, PhD

Nine months before presentation, a 29-year-old patient had his university studies interrupted because of a 1-month psychiatric hospital admission for a first episode of psychosis. His auditory hallucinations and grandiose delusions had improved on oral risperidone (4 mg/d), but he had abruptly stopped taking it because of weight gain 3 months later. He had subsequently deteriorated over the next month, with an exacerbation of psychosis, and had agreed to take aripiprazole. He had been on 15 mg of aripiprazole for the 6 months before presentation, had returned to the university and had managed his weight. He had decided to stop all antipsychotics as he felt fully well except for some fatigue.

On examination, he had no features of depression or mania. His scores on the 6 items of the Positive and Negative Syndrome Scale (PANSS) were all less than 3. He was keen to return to his life before antipsychotics. When we highlighted the higher risk of relapse upon discontinuation in the early phases of psychosis, he appreciated the reasoning but pointed out the pervasive lethargy and argued that he was likely to be among the minority who would not relapse. Considering the risk of complete therapeutic disengagement, we prepared a titration and monitoring plan, to which he agreed, and offered to maintain monthly contact with the nurse case manager.

This case raises a widespread therapeutic dilemma faced by clinicians treating patients in the early stages of psychosis. Although several guidelines recommend uninterrupted treatment for the first 2 years of schizophrenia (i.e., 18 months after the resolution of positive symptoms),[1] a firm diagnosis of schizophrenia is often not made in first-episode settings. Even when the diagnostic picture is clear, patients perceive the negative effects of antipsychotics to be more severe when active psychotic symptoms have resolved.[2] Recent evidence in favour of continued use of antipsychotics for up to 5 years after the first episode of schizophrenia to reduce the risk of relapse,[3] symptom exacerbation,[4] death[5] and work disability[6] is robust. Nevertheless, in practice, patients prioritize day-to-day well-being over the risk of future events such as relapse or death.[7] For those in the early phase of illness, a repeated cycle of interruption and reintroduction is the norm rather than the exception. Nearly 50%–60% of patients in some first-episode settings discontinue their antipsychotics within 2 years,[8,9] generally after 6 months of treatment, with more than 45% relapsing in the next 18 months.[9] One study involving a national cohort identified a median of 6 interruptions over 8 years of follow-up.[10] The development and implementation of tools for personalized risk estimations upon discontinuation are important, but given the high prevalence, the most pertinent clinical question is how to guide safe discontinuation within an early intervention setting when patients make such a decision.

Patients who appreciate the ongoing risk of relapse may still wish to test the hypothesis that they no longer need medication, as was the case with our patient. Discussion of the optimal timing and duration of the discontinuation trial and of frequency of monitoring (e.g., measurement of key symptom and functioning domains) is often helpful in such cases. Successful discontinuation is more likely in the absence of schizophrenia and substance use disorders, among patients who achieve premorbid (or satisfactory) levels of functioning and clinical remission (as with our patient) and when a good degree of social support is in place.[11] There are no clear guidelines on when to implement a discontinuation trial, but the presence of more than the minimal burden of psychotic symptoms should prompt a delay or reconsideration. Reinstituting treatment after a relapse appears to be associated with a diminished response that takes longer to occur.[12]

For some patients, discontinuation may induce cholinergic (often gastrointestinal) or dopaminergic (e.g., akathisia, movement disorders) withdrawal symptoms. Although the risk of relapse is highest in the first few months after stopping oral antipsychotics, a gradual worsening of symptoms may occur over longer periods.[4] A recent proposal advocates for hyperbolic tapering over several months;[13] the acceptability of such extended tapering in first-episode settings is yet to be evaluated. Given the lack of data for a firm recommendation, the best approach for tapering is likely to be one of a shared decision between the patient and the prescriber after acknowledging the uncertainties. Some antipsychotics (e.g., partial dopamine agonists, long-acting injections with long half-lives) may have less propensity to cause withdrawal syndromes.

It is risky to discontinue antipsychotics in first-episode settings, but it is a choice often made by patients. Many of the risks can be mitigated by enhanced clinical support, which may not be available in some settings.[14] To reduce concerns of family members of patients undergoing discontinuation trials,[15] it is crucial to develop an inventory of early warning signs of exacerbation (e.g., sleep disturbances, disorganized speech), enhance nonpharmacological support and maintain a positive therapeutic relationship and self-care during the discontinuation trial.[16] The prescribing process (i.e., information exchanged and uncertainties discussed) is a key variable in the overall

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outcome, especially among patients who face negative experiences when seeking care.[17] In the absence of reliable, person-specific indicators of an impending relapse, individualized plans of collaborative antipsychotic discontinuation are necessary for optimal early intervention for psychosis.

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Conclusion

La prise en charge des premiers épisodes psychotiques représente un **défi clinique et thérapeutique majeur**.

Notre travail a exploré plusieurs axes pour une approche plus efficace et personnalisée : la pharmacogénétique, la motivation du patient, les dysfonctions sexuelles, et la durée des traitements antipsychotiques.

L'interdépendance de ces éléments souligne certains aspects importants de la psychiatrie actuelle. Pour appréhender efficacement les troubles schizophréniques débutants, une stratégie multidimensionnelle est indispensable. Cette **conception holistique** de la santé mentale, où chaque facteur interagit avec les autres pour influencer le parcours de soin et le pronostic du patient, est particulièrement pertinente dans la prise en charge des troubles psychotiques débutants.

L'étude de la pharmacogénétique permet de souligner l'importance de la **personnalisation du traitement pharmacologique**. En analysant le profil génétique d'un individu, cette discipline offre des clés pour prédire la réaction aux médicaments antipsychotiques, optimisant ainsi l'efficacité du traitement tout en minimisant les risques d'effets indésirables. Cette démarche est essentielle, car elle reconnaît l'unicité biologique de chaque patient, posant les bases d'une prise en charge adaptée dès le début. L'identification précoce des patients à risque de non-réponse à certains médicaments ou susceptibles de développer des effets secondaires graves comme le risque accru de suicide renforce la nécessité de cette approche.
Nous avons aussi vu comment les prescriptions précoces de clozapine pourraient concourir à une amélioration globale de la prise en charge des premiers épisodes, notamment via une réduction des idées suicidaires.

La motivation du patient, étroitement liée à l'absence d'effet indésirable du traitement, prend ici tout son sens. Un patient informé et impliqué dans les décisions thérapeutiques est plus à même de s'engager dans le processus de guérison. La pharmacogénétique, en offrant des options **thérapeutiques personnalisées**, peut donc augmenter le sentiment d'empowerment du patient. Ce lien entre la personnalisation du traitement et la motivation du patient est crucial, car une adhésion optimale au traitement est souvent le pilier d'un pronostic favorable et d'une alliance thérapeutique de qualité. La motivation est également renforcée par le soutien psychosocial et les stratégies thérapeutiques ciblées, soulignant là encore l'importance d'une prise en charge globale.

Les dysfonctions sexuelles, fréquemment rencontrées chez les patients atteints de troubles schizophréniques, constituent un obstacle majeur à la **qualité de vie** et à l'acceptation du traitement. Cette problématique, bien que complexe, est aussi liée à la pharmacogénétique (notamment avec la prévention des effets indésirables sexuels) avec un impact direct sur la motivation. Les effets secondaires des antipsychotiques, pouvant inclure des dysfonctions sexuelles, mettent en lumière le besoin d'une sélection soignée des médicaments, basée sur le profil génétique du patient. Une communication ouverte et empathique à ce sujet est donc essentielle pour maintenir l'engagement du patient dans son parcours de soin.

La décision concernant la durée du traitement et son arrêt ne peut être prise isolément par le psychiatre, mais doit considérer les aspects pharmacogénétiques, la motivation et le bien-être global du patient, y compris sa vie sexuelle. Une approche flexible et personnalisée, ajustant la durée du traitement en fonction des besoins spécifiques et des préférences du patient, peut renforcer **l'alliance thérapeutique** et l'adhésion au traitement à long terme. Cette flexibilité, loin d'être un signe d'incertitude, reflète une compréhension approfondie des nuances de la prise en charge psychiatrique, où le patient est véritablement au cœur du processus décisionnel.

En conclusion, la prise en charge des premiers épisodes psychotiques dans les troubles schizophréniques nécessite une approche intégrée et personnalisée, où la pharmacogénétique, la motivation du patient, la gestion des dysfonctions sexuelles, et la flexibilité de la durée des traitements sont envisagées comme un tout cohérent.

Ce n'est qu'en reconnaissant et en adressant l'interconnexion entre ces divers aspects que nous pouvons aspirer à une prise en charge efficace et respectueuse des besoins uniques de chaque patient. Cette vision holistique est essentielle pour avancer vers une psychiatrie plus humaine et personnalisée, capable de répondre de manière optimale aux défis posés par la prise en charge des premiers épisodes psychotiques.

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