INPLASY PROTOCOL

To cite: Merino et al. Protocol: Adverse Drug Reactions of Olanzapine, Clozapine and Loxapine in Children and Youth: A Systematic Pharmacogenetic Review. Inplasy protocol 202250025. doi: 10.37766/inplasy2022.5.0025

Received: 04 May 2022

Published: 04 May 2022

Corresponding author:
Susanne Thümmler

thummler.s@pediatrie-chulenval-nice.fr

Author Affiliation:
Children's Hospitals of Nice CHU-Lenval, Nice, France.

Support: **None.**

Conflicts of interest:
None declared.

Protocol: Adverse Drug Reactions of Olanzapine, Clozapine and Loxapine in Children and Youth: A Systematic Pharmacogenetic Review

Merino, D[1]; Fernandez, A[2]; Gérard, AO[3]; Ben Othman, N[4]; Rocher, F[5]; Askenazy, F[6]; Verstuyft, C[7]; Drici, MD[8]; Thümmler, S[9].

Review question / Objective: **In children and youth treated with olanzapine, clozapine, or loxapine and having undergone genotyping, which are the pharmacogenetic variants underlying the antipsychotics' adverse drug reactions and efficacy? What are the most frequently investigated adverse drug reactions and variants ? What is described about the specific effect of CYP1A2 variants ? Therefore, we aimed to review the pharmacogenetic variants underlying olanzapine, clozapine and loxapine ADRs and/or efficacy, in children and youth having undergone genotyping. Then, assessed the most frequently investigated ADRs and genetic polymorphisms in this population. Finally, we investigated the specific effect of CYP1A2 variants in the occurrence of ADRs and/or lack of therapeutic effect.**
Condition being studied: **This review focuses on children, adolescents and youth treated with antipsychotics (olanzapine, clozapine, loxapine) and experienced adverse drug reactions.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 04 May 2022 and was last updated on 04 May 2022 (registration number INPLASY202250025).

INTRODUCTION

Review question / Objective: **In children and youth treated with olanzapine, clozapine, or loxapine and having undergone genotyping, which are the pharmacogenetic variants underlying the antipsychotics' adverse drug reactions and efficacy? What are the most frequently investigated adverse drug reactions and variants ? What is described about the specific effect of CYP1A2 variants ? Therefore, we aimed to review the pharmacogenetic variants underlying olanzapine, clozapine and loxapine ADRs and/or efficacy, in children and youth**

having undergone genotyping. Then, assessed the most frequently investigated ADRs and genetic polymorphisms in this population. Finally, we investigated the specific effect of CYP1A2 variants in the occurrence of ADRs and/or lack of therapeutic effect.

Rationale: In child psychiatry, antipsychotic drugs (APs) are used to treat psychotic or mood disorders, as well as behavioral symptoms, despite limited evidence. Although APs are usually efficacious, the risk of adverse drug reactions (ADRs) should be considered when initiating APs in this population. Treatment resistance is also a major concern. Many factors may influence the pharmacokinetics and pharmacodynamics of APs, such as sex, ancestry, puberty, dietary and smoking habits, potentially leading to ADRs or lack of therapeutic effects. The cytochrome P450 (CYP) proteins, a superfamily of liver enzymes, are instrumental to drug metabolism. At least 57 human CYPs have been described, even if most reactions are undertaken by CYP2C9, CYP2C19, CYP2D6 and CYP3A4. Major interindividual differences in their expression arise from genetic polymorphisms, leading to various metabolizing phenotypes which determine the CYPs levels of activity. Alterations in their activity by extrinsic inducers or inhibitors, can imbalance a well-tolerated treatment; or potentiate a given medication. As CYP metabolize most APs, some studies addressed the potential consequences of CYP2D6 polymorphisms in children and youth treated with APs. While CYP1A2 represents approximately 15% of hepatic CYP content, it is pivotal in the metabolism of the two atypical APs olanzapine and clozapine, as well as loxapine (which properties are closely related to those of atypical APs). Olanzapine and clozapine are used as second to third-line therapy, while loxapine may allow symptomatic relief of acute agitation. In child psychiatry, the Food and Drug Administration (FDA) has granted marketing authorization for olanzapine in acute mixed or manic episodes of bipolar I disorder and treatment of schizophrenia for adolescents aged from 13 to 17 years old. Similarly, the FDA authorized use of olanzapine in cases of depressed bipolar I disorder, in combination with fluoxetine, in children and adolescents aged between 10 to 17 years old. By contrast, the European Medicines Agency (EMA) did not recommend olanzapine for use in children and adolescents below 18 years of age. Regarding clozapine, its therapeutic indications are mainly represented by treatment-resistant schizophrenia and recurrent suicidal behaviors in schizophrenic disorders, without prejudice to the age. The EMA stated that safety and efficacy of clozapine in children under the age of 16 have not been established yet. Likewise, regarding loxapine, both FDA and EMA mentioned that safety and effectiveness in pediatric patients have not been established. However, in France, the National Drug Agency (Agence Nationale de Sécurité du Médicament et des produits de santé (ANSM)) granted authorization for loxapine in the treatment of acute and chronic psychotic disorders as from the age of 15 years. Atypical APs tend to induce less extrapyramidal effects, and may therefore be the preferred option when treating children and youth. However, their profile comes at the price of other prominent ADRs, such as metabolic changes. As they begin in childhood, they are likely to persist over lifetime. Children are also exposed to a plethora of ADRs, such as neuroleptic malignant syndrome, seizures, agranulocytosis, or hyperprolactinemia. The safety profile of olanzapine and clozapine shows major issues of concern; and the tolerability of loxapine scarcely investigated. Increased knowledge of the determinants of each patient's exposure to APs could pave the way to tailored therapy. Pharmacogenetics consists of the study of how genetic differences influence the variability in patient's responses to drugs. Genome-wide association studies, candidate gene studies, whole-genome sequencing and assessment of cytochrome's phenotypes brought us closer to personalized medicine, whereby the understanding of each patient's genetic profile may predict the occurrence of ADRs or lack of effect. This may be especially useful in specific

populations, often excluded of clinical trials and the classical field of evidence-based medicine.

Condition being studied: This review focuses on children, adolescents and youth treated with antipsychotics (olanzapine, clozapine, loxapine) and experienced adverse drug reactions.

METHODS

Search strategy: Two authors (D.M. and A.O.G) separately conducted the research in four electronic bibliographic databases: PubMed, EMBASE, PsycINFO, and PsycArticles. The search strategy included terms defining the population, the exposure, the intervention, and the potential outcome. The search strategy (including keywords) for PubMed was: "((((adolescent* OR youth OR child* OR pedia* OR paedia*) AND (clozapine OR olanzapine OR loxapine) 584 AND (pharmacogen* OR allele OR genotype* OR cytochrome* OR CYP1* OR CYP2* OR CYP3* OR CYP4*) AND (adverse drug reaction* OR adverse event* OR adverse reaction* OR side effect* OR secondary effect* OR after effect* OR tolerability OR safety))))). We restricted the research to English-language publications. Our query retrieved publications registered in the four selected databases up to March 21, 2022.

Participant or population: Data extraction relied on the following inclusion criteria:1. Studies including at least one child and/or adolescent and/or youth, therefore aged under 25, following the United Nations definition.2. Receiving at least one atypical antipsychotic which is metabolized by CYP1A2 (clozapine, olanzapine, loxapine). Considering the foreseeable paucity of evidence informing the review, we have chosen to keep studies including 'mixed' (both adult and pediatric) populations, with due regard to the age criterion: 'Studies including at least one child and/or adolescent, therefore aged under 25'.

Intervention: Inclusion criteria (continued): 3. Having experienced an adverse drug reaction/ a lack of therapeutic effect linked to at least one of these treatments 4. Having undergone pharmacogenomic analysis/ genotyping, which results are mentioned.

Comparator: Groups with different genotype/ outcome (e.g. lack of adverse drug reaction, adequate therapeutic response).

Study designs to be included: We excluded books (and chapters), commentaries, systematic reviews, meta-analyses. However, considering the foreseeable paucity of evidence informing the review, we decided to include conference abstracts and editorial pieces.

Eligibility criteria: Inclusion criteria: 1. Studies including at least one child and/or adolescent and/or youth, therefore aged under 25, following the United Nations definition.2. Receiving at least one atypical antipsychotic which is metabolized by CYP1A2 (clozapine, olanzapine, loxapine)3. Having experienced an adverse drug reaction/ a lack of therapeutic effect linked to at least one of these treatments 4. Having undergone pharmacogenomic analysis/ genotyping, which results are mentioned. Considering the foreseeable paucity of evidence informing the review, we have chosen to keep studies including 'mixed' (both adult and pediatric) populations, with due regard to the age criterion: 'Studies including at least one child and/or adolescent, therefore aged under 25'.

Information sources: Two authors (D.M. and A.O.G) separately conducted the research in four electronic bibliographic databases: PubMed, EMBASE, PsycINFO, and PsycArticles up to March 21, 2022.

Main outcome(s): - Variants favouring/ lowering the risk of a given adverse drug reaction or lack of therapeutic effect in children and youth treated with olanzapine, clozapine, or loxapine. - Strength of association between the frequency of a variant/allele in a group and the occurence

of an adverse drug reaction or a lack of therapeutic effect.

Additional outcome(s): - Variants/type of genetic analyses most frequently performed when looking for an association with an adverse drug reaction or a lack of therapeutic effect. - Situations in which CYP1A2 are documented: which adverse drug reactions are concerned and which variants/phenotypes may be associated with adverse drug reactions/ lack of therapeutic effect.

Data management: Manual screening has been used. Next, inclusion of the selected articles in Microsoft Excel® worksheets and in a Zotero® folder have been performed. Quality assessment have been performed using Microsoft Excel® worksheets.

Quality assessment / Risk of bias analysis: The quality of the included pharmacogenetic studies have been independently assessed by D.M. and A.O.G, relying on a tool adapted from Maruf et al. and the checklist developed by Jorgensen and Williamson. The following issues of concern will be addressed:
1. Choosing the genes/ SNPs to genotype (4 binary questions)
2. Sample size (3 questions: 2 binary, 1 open)
3. Study design (1 open question)
4. Reliability of genotypes (5 binary questions)
5. Missing genotype data (6 binary questions)
6. Population stratification (2 binary questions)
7. Hardy-Weinberg Equilibrium (2 binary questions)
8. Choice and definition of outcomes (3 binary questions)
The purpose of open questions (sample size; study design) was to allow a quality visual check as a complement to the global score of each publication.For each binary question, we answered:
• 'Yes' if the study provided an adequate response
• 'No' if the response was not mentioned in the manuscript nor a method publication referenced by the authors
• 'N/A' (Not Applicable) if the response to the main (first) question of the issue of concern addressed is 'No'.
Consequently, each study received a quality score comprised between 0 and 24, based on the summation of the 'Yes' answers. According to this approach, the higher the score, the higher the quality of a given study.
Any case of discrepancy between their assessments have been resolved through discussion.
We anticipated differences in general characteristics (e.g. methodology, sample size) of the studies between the two categories (pediatric and mixed population studies), and in pharmacogenetic findings as well (due to metabolic specificities expected in children). Meta-biases have been visually checked (and grouped via the quality assessement), and therefore reported in the discussion section.

Strategy of data synthesis: We distinguished - 'pediatric studies' in which all participants are aged under 25 - 'mixed population studies', including a share of patients aged under 25, but also adults or elderly people.
We provided :
- regarding characteristics of the studies: a synthesis of pediatric studies' characteristics and a synthesis of mixed population studies' characteristics (study type, sample size, age range, main ancestry, antipsychotic, adverse drug reaction, quality assessment)
- regarding outcomes: we synthesized studies investigating similar adverse drug reactions and/or similar genotyping approaches.

Subgroup analysis: Studies have been classified according to their methodology: case reports or case series, cohort studies, and case-control (or cross-sectional) studies. We will distinguish 'pediatric' studies, exclusively relying on pediatric samples, and 'mixed population' studies, to present their respective characteristics and quality assessments. Then, the whole studies will be grouped according to the main classes of ADRs investigated.

Sensitivity analysis: Non applicable.

Language: English.

Country(ies) involved: France.

Other relevant information: Only few studies have been published yet regarding the issues addressed by our review. Therefore, we expected to encounter difficulties in finding enough studies to screen for the review. Indeed, whe had to try different queries in order to choose the one that provided the best compromise with enough specificity, as well as a sufficient number of studies to screen and include. Further, we needed to extract the majority of data among all studies (therefore, to consider the results of the review) to define our subgroups ('pediatric studies' and 'mixed population studies'), our data synthesis strategy (e.g. which genes or which ADR), and to refine the quality assessment method we relied on. In this context, the full protocol could not be prospectively registered, because of the foreseeable lack of anticipation of our included studies proper characteristics.

Keywords: systematic review; child; children; adolescent; youth; adverse drug reaction; side effect; pharmacoresistance; olanzapine; clozapine; loxapine; antipsychotics; CYP1A2.

Dissemination plans: We submitted our review to a journal on Wednesday, 27 April 2022.

Contributions of each author:

Author 1 - Diane Merino - D.M contributed to conceptualization, methodology, validation, formal analysis, investigation, resources, data curation, , visualization, writing (original draft preparation) and project administration of the manuscript.
Email: merino.d@chu-nice.fr
Author 2 - Arnaud Fernandez - A.F. contributed to conceptualization and writing (review and editing) of the manuscript.
Email: fernandez.a@pediatrie-chulenval-nice.fr
Author 3 - Alexandre Gérard - A.G. contributed to methodology, validation, formal analysis, investigation, resources, data curation and writing (original draft perparation) of the manuscript.
Email:gerard.a@chu-nice.fr
Author 4 - Nouha Ben Othman - N. BO. contributed to formal analysis, investigation, resources, and data curation.
Email: ben-othman.n@chu-nice.fr
Author 5 - Fanny Rocher - F.R. contributed to writing (review and editing).
Email: rocher.f@chu-nice.fr
Author 6 - Florence Askenazy - F.A. contributed to writing (review and editing).
Email: askenazy.f@pediatrie-chulenval-nice.fr
Author 7 - Céline Verstuyft - C.V. contributed to methodology and writing (review and editing).
Email: celine.verstuyft@aphp.fr
Author 8 - Milou-Daniel Drici - MD.D. contributed to validation, writing (review and editing), and supervision of the manuscript.
Email: pharmacovigilance@chu-nice.fr
Author 9 - Susanne Thümmler - S.T. contributed to conceptualization, methodology, validation, writing (original draft preparation and review, editing), visualization, supervision and project administration.
Email: thummler.s@pediatrie-chulenval-nice.fr

Review Stage at time of this submission: The review is completed and submitted, but not published yet. Only few studies have been published yet regarding the issues addressed by our review. Therefore, we expected to encounter difficulties in finding enough studies to screen for the review. Indeed, whe had to try different queries in order to choose the one that provided the best compromise with enough specificity, as well as a sufficient number of studies to screen and include. Further, we needed to extract the majority of data among all studies (therefore, to consider the results of the review) to define our subgroups ('pediatric studies' and 'mixed population studies'), our data synthesis strategy (e.g. which genes or which ADR), and to refine the quality assessment

method we relied on. In this context, the full protocol could not be prospectively registered, because of the foreseeable lack of anticipation of our included studies proper characteristics.