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ATYPICAL ANTIPSYCHOTICS FOR SCHIZOPHRENIA AND/OR BIPOLAR DISORDER IN PREGNANCY: CURRENT RECOMMENDATIONS AND UPDATES IN THE NICE GUIDELINES

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SUMMARY

Background: *The gold standard pharmacological agents used to treat schizophrenia and bipolar disorder in adults are antipsychotics. Atypical or second-generation antipsychotics have superseded or used as alternatives to typical first-generation antipsychotics due to better tolerability and safety profile. However the efficacy and safety of these drugs are severely limited in pregnancy and/or women of childbearing potential. There are very few guidelines to guide the clinical management of schizophrenia and/or bipolar disorder in this subgroup.*

Aim: *We aimed to review current evidence of atypical antipsychotics used in pregnancy where available, with considerations to its efficacy and safety to both the mother and fetus, in conjunction with the recently updated NICE guidelines.*

Methods: *The latest NICE CG192 guidelines on antenatal and postnatal mental health, published in December 2014 was reviewed and summarized, and the BNF-approved list of atypical antipsychotics were identified. Clinically relevant MEDLINE-linked publications were searched and selected where available using the PubMed search engine to identify evidence for or against the use of atypical antipsychotics in pregnancy.*

Results and Conclusions: *NICE CG192 improved clarity on the prediction, support and holistic management of mental illness in pregnancy and puerperium; however there were no specific recommendations in terms of pharmacological agents used to treat schizophrenia and/or bipolar disorder in this subgroup. Evidence from the literature on atypical antipsychotics yielded discordant results. Nonetheless, our report presents preliminary findings of certain antipsychotics which appear to be effective and safe in pregnancy. Future research would benefit from larger, prospective randomized controlled trials, and perhaps include newer atypical antipsychotics for consideration in this subgroup.*

Key words: *atypical antipsychotics – pregnancy – schizophrenia - bipolar*

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INTRODUCTION

Schizophrenia and bipolar disorder pose significant morbidity and mortality to those affected and inadequate control may lead to detrimental effects (Goff 2005, Smith 2013).Currently, antipsychotics coupled with psychological interventions are first line in the treatment of schizophrenia and bipolar disorder (NICE 2014). The development of second generation or atypical antipsychotics improved efficacy, whilst minimizing extrapyramidal side-effects; although metabolic adversities such as obesity and Type II diabetes have now been reported (Newcomer 2006). Further barriers need to be overcome when treating pregnant women and women of childbearing age, particularly when considering the risk: benefit ratio to both the mother and child. The right balance must be struck to ensure the quality of life of the patient against potential teratogenic effects on the unborn fetus. Teratogenic effects have been identified in first-generation or typical antipsychotics such as phenothiazine and haloperidol given during the first trimester of pregnancy, however much less is known about the newer atypical antipsychotics (Godes 1991, Edlund 1984). Although there has been a trend towards increased use of atypical antipsychotics during pregnancy, our understanding of the effectiveness and safety profile of these drugs remain severely lacking, hampering the identification of an optimal management strategy for these patients (Toh 2013). Ethical restrictions further limit the high-quality research that needs to be conducted in order to answer these questions.

The National Institute of Health and Care Excellence (NICE) had updated their guidelines on the management of antenatal and postnatal mental health as recently as December 2014. We review the current updates in the NICE guidelines with a particular focus on atypical antipsychotics in conjunction with the NICE guidelines on the management of schizophrenia and bipolar disorder in adults, with the aim of providing better guidance to both clinicians and pregnant service users considering the use of antipsychotics.

METHODS

A review was conducted focusing on atypical or second-generation antipsychotics in two psychiatric conditions: schizophrenia and bipolar disorder, of which, a small subgroup notably pregnant women and women of childbearing age formed the crux of our study. Comparisons were made using the previous and current National Institute for Health and Care Excellence (NICE) guidelines for the relevant conditions associated with maternal care, in addition to a review of the British National Formulary (BNF). Subsequently, a highly

sensitive list of all MEDLINE-indexed trials were searched using PubMed, MEDLINE, EMBASE and PsychInfo databases, with the search terms 'atypical antipsychotic* (MESH)', and 'bipolar*' or 'schizophrenia*' in the article title, abstract or keywords. Full text publications in English Language were selected to include adult human populations, further restricted to 'women of childbearing age*' OR 'pregnan*'. The search criteria prioritized articles of high clinical relevance i.e. evaluating the use of atypical antipsychotics in pregnant women or women of childbearing age, of which, efficacy and safety profiles were sought.

CURRENT GUIDELINES (DECEMBER 2014)

NICE guidelines

NICE guidelines (CG192) have enhanced NICE (CG45 and CG62), published in February 2007 and March 2008 on good antenatal and postnatal care in patients with mental health disorders. A great emphasis has shifted towards the impact of mental health illness on parenting, risks to the fetus and baby; in addition to better prediction, detection and management routes and referrals with respect to specific mental health issues in pregnancy and in the postnatal period. Key changes and updates in the pharmacological management of pregnant women with bipolar disorder and schizophrenia are summarized in Table 1.

Table 2 illustrates the current pharmacological agents recommended by NICE in the management of schizophrenia and bipolar disorder in adults. Although there were no suggestions on specific antipsychotics for schizophrenia, NICE CG178 listed some guidelines to which both clinicians and service users base their decision making on. There was a focus towards weighing the potential benefits and adverse events including metabolic (weight gain and diabetes), extrapyramidal (including akathisia, dyskinesia and dystonia), cardiovascular (prolonged QT interval), hormonal (increased prolactin levels), and others (unpleasant subjective experiences) (NICE CG178, 2014).

Table 1. Key updates in the pharmacological aspects of NICE guidelines on Antenatal and postnatal mental health: clinical management and service guidance

Changes	NICE CG192 (December 2014)
Starting, using and stopping treatment	▪ Measure prolactin levels in patients taking prolactin-raising antipsychotics; if raised, consider prolactin-sparing antipsychotic: ▪ Continue antipsychotic if she is likely to relapse without medication; ▪ Do not offer depot antipsychotics in women who are planning a pregnancy, pregnant or considering breastfeeding, unless she is responding well to depot and has previous history of non-adherence to oral medication; ▪ Do not offer valproate in the treatment of mental health problem in women of childbearing potential;
Interventions for severe mental illness	▪ Consider structured specific psychological interventions when medication is changed or stopped; ▪ Offer an antipsychotic if a pregnant woman develops mania/psychosis and not taking psychotropic medication; ▪ Offer antipsychotic in line with NICE CG185 on bipolar disorder as prophylactic medication in pregnant women stopping lithium or planning to breastfeed.; ▪ Development of mania in a pregnant woman taking prophylactic medication at optimal dose: change antipsychotic to another type of prophylactic drug, consider lithium if unresponsive, and consider electroconvulsive therapy (ECT) if there has been no response to lithium;
Electroconvulsive therapy (ECT)	▪ Consider ECT in pregnant women with severe depression, severe mixed affective states or mania, or catatonia, whose physical health or fetus is at serious risk;
Treatment in the Postnatal period	▪ Encourage breastfeeding unless patients are taking carbamazepine, clozapine or lithium; ▪ The level of antipsychotic medication in breast milk depends on the drug; ▪ Monitor the baby for adverse effects.

Table 2. Current Pharmacological Recommendations by NICE in the Treatment of Schizophrenia and Bipolar Disorder. (NICE CG178 and NICE CG185)

Disorder	Current Pharmacological Recommendations
Schizophrenia (NICE CG178)	First episode psychosis: No specific antipsychotic was recommended Non-responsive/Resistant illness: clozapine
Bipolar Disorder (NICE CG185)	Mania: Lithium*, haloperidol, olanzapine, quetiapine, risperidone Moderate/Severe Depression: fluoxetine and olanzapine, or quetiapine alone, consider lamotrigine Long term management: Lithium*, valproate, olanzapine

* indicates first line treatment

The British National Formulary (BNF) 4.2.1 lists various antipsychotic drugs used for various conditions. Of note, approved atypical antipsychotic drugs include amisulpride, aripiprazole, clozapine, lurasidone, olanzapine, paliperidone, quetiapine, risperidone. The BNF also cautions against extrapyramidal effects and withdrawal syndrome in neonates following maternal use of antipsychotics in the third trimester of pregnancy, although the causative antipsychotics were not detailed (BNF 2015).

SUMMARY OF RESULTS

Table 3 summarizes the representative findings of our report where clinical data was available.

Table 3. Summary of Clinically Available Data on Pregnancy-related Outcomes of Atypical Antipsychotics

Atypical Antipsychotic	Study	Reproductive Issues
Paliperidone	Ozdemir et al. 2015	▪ Case Report: no congenital anomalies detected at 4 months of follow-up, although efficacy was questionable in pregnancy.
Risperidone	McKenna et al. 2005	▪ No increased risk of fetal malformations (n=49).
	Ennis et al. 2015	▪ Cumulative data (systematic review): 22/432 (5.1%) malformation rate in those exposed to risperidone in the 1st trimester (no suggestion of significantly increased risk)
	Chatterjee and Sharan 2014	▪ Case report: temporal association between tardive dyskinesia with risperidone at the onset of pregnancy; hypothesized to be due to the sensitizing effect of oestrogen status in pregnancy, although withdrawal effects from olanzapine and quetiapine could not be excluded
Olanzapine	Goldstein et al. 2000	▪ Small prospective surveys (n=23): No increased risk of spontaneous abortion, stillbirth, prematurity or major malformation in offspring exposed to olanzapine in pregnancy. No risk of lactation and perinatal withdrawals reported, although these findings are subject to risk of bias.
	McKenna et al. 2005	▪ No significantly increased risk of fetal malformations, although the incidence of low birth weight and therapeutic abortions were high. (n=60)
	Ennis et al. 2015	▪ Large cumulative data (systematic review): 38/1090 (3.5%) malformation rate in those who received olanzapine in the first trimester (no increased risk).
	Pipasha et al. 2001	▪ However, a post-marketing surveillance study (n=8588) identified a single report (1/18) of therapeutic abortion due to lumbar myelomeningocoele in the fetus.
	Newport et al. 2007	▪ The rate of placental transfer of olanzapine was significantly high albeit incomplete compared to other antipsychotics (mean=72.1%, SD=42%) in a prospective observational study.
		▪ In addition, there were high rates of low birth weights and critical care admissions, although this was not statistically significant.
	Boden et al. 2012	▪ Higher risk of gestational diabetes, however the risks were not significant after adjusting for early pregnancy Body Mass Index (BMI).
Quetiapine	Newport et al. 2007	▪ An observational study found quetiapine to show the lowest rate of placental passage (compared to olanzapine, risperidone and haloperidol) (mean=23.8%, SD=11%).
	Taylor et al. 2003	▪ Case Report: Efficacy (remission of psychosis) and safety in pregnancy and perinatally, with decreased risk of sexual and extrapyramidal side effects.
	Gentile 2006	▪ Case Report: Combination of quetiapine-fluvoxamine is safe for both the mother and child, with no increased risk of fetal malformations compared to the general population. No developmental abnormalities were noted.
	Ennis et al. 2015	▪ Large cumulative data (systematic review): 16/443 (3.6%) malformation rate in first trimester exposed mothers (no suggestion of significantly increased risk)
Aripiprazole	Gentile et al. 2011	▪ Case Report and Literature Review: No obstetric* and neonatal complications followed up at 8 weeks after delivery, however suggests an increased risk of perinatal arrhythmias if aripiprazole is given in the third trimester.
	Gentile 2010	▪ Case Report: Aripiprazole prescribed throughout pregnancy did not result in maternal adverse events, or teratogenicity, toxicity, growth retardation and neurobehaviouralabnomalities in the fetus. Lactation however failed to be established postnatally, which was hypothesized to be the result of interactions of aripiprazole with prolactin release.
	Mendhekar et al. 2006	
	Ennis et al. 2015	▪ Cumulative data (systematic review): 5/100 (5%) malformation rate in those who had 1st trimester exposure to aripiprazole (numbers were too low to generate significant conclusions)

Table 3. Continues

Atypical Antipsychotic	Study	Reproductive Issues
Clozapine	Gentile 2010	▪ Discordant results on safety of clozapine, with more cases reporting major malformations, obstetric*, perinatal and metabolic adversities
	Boden et al. 2012	▪ Higher risk of gestational diabetes, however the risks were not significant after adjusting for early pregnancy Body Mass Index (BMI)
Asenapine	Gentile 2010	▪ Unknown teratogenic risk
Ziprasidone	Gentile 2010	▪ Unknown teratogenic risk
	Peitl et al. 2010	▪ Case report: cleft lip/palate in a patient on ziprasidone treatment throughout pregnancy
	Werremyer and Pharm 2009	▪ Case report: no behavioural teratogenicity or pregnancy-associated complications in a patient taking ziprasidone and citalopram throughout pregnancy and postnatally.
Lurasidone	No available study	▪ Unknown teratogenic risk. No pregnancy-associated outcome measures/trials in humans
Amisulpride	Gentile 2010	▪ Unknown teratogenic risk

*Obstetric complications of concern included neonatal intensive care admissions, cardio-respiratory complications, low/high birth weight babies and/or prematurity, neonatal withdrawal syndrome, gestational metabolic adverse effects, and teratogenicity, among others.

DISCUSSION

Clearly defined guidelines are needed for pregnant and/or women of childbearing potential due to the increased frequency of unplanned pregnancies in those with schizophrenia and/or bipolar disorder (Miller and Finnrerty 1996). NICE CG192guidelines provide improved clarity in terms of the management, support and monitoring of mental health disorders and potential adverse effects of pharmacological agents in women of childbearing age both in the antenatal and postnatal period. The overarching viewpoint remains to encourage psychological interventions as first-line wherever possible, in order to minimize risks to the mother and child, with a consideration for pharmacological therapy (Table 1) starting with the safest and lowest dose, should patients remain symptomatic.

However NICE CG192 still lacks specific therapeutic recommendations for each disorder for this subset of patients, even when signposted to the NICE guidelines for the management of schizophrenia (CG178) and bipolar disorder (CG185) respectively. This could be due to the limited number and power of efficacy-safety trials in addition to the wide range of responsiveness in this subgroup of patients. However, equally, emphasis is placed on the joint decision making by both physicians and service users with continuous adjustments of treatment regimen should the current regimen be unsuitable; thus making a single antipsychotic recommendation difficult.

Atypical antipsychotics have been known to be associated with metabolic complications – weight gain and Type II diabetes to name a few. However, adverse events of atypical antipsychotics in association with pregnancy have not been clearly elucidated. A recent report by Jayashri et al. 2015 states that the most commonly prescribed atypical antipsychotics in pregnancy (olanzapine, quetiapine, risperidone) do not confer an increased risk of congenital detriment and malformation in the fetus (Jayashri et al. 2015). Overall, the results from our study were discrepant. A population cohort comparison study found no significant differences in major malformations between those who received atypical antipsychotics (olanzapine, risperidone, quetiapine, clozapine) and those without, except the frequency of low birth weight and therapeutic abortions, although these results were not investigated with individual agents (McKenna 2005). Another large population based study found that the risk of having small-for-gestational age infants were elevated, however this was not statistically significant after accounting for maternal factors (Boden 2012). Furthermore, preliminary findings show promise with quetiapine as it appears safe to both the mother and fetus, nonetheless these results should be confirmed with larger and more standardized trials. (Newport 2007, Taylor 2003, Gentile 2006).

Conversely, a systematic review demonstrated increased risk of pregnancy-related metabolic complications (gestational diabetes, obesity), birth defects and rate of large-for-gestation babies with specific atypical antipsychotics (Gentile 2010). Given the known side-effect profile of second-generation antipsychotics however, it is difficult to pinpoint whether the metabolic complications would have occurred independently of pregnancy. Indeed, the risks of obstetric complications are higher in women with metabolic derangements, regardless of whether she suffers from a psychiatric illness. Still, Boden et al. 2012 showed that the incidence of gestational diabetes were more than double in mothers who used antipsychotics than those without (4.2% vs. 1.7%) (Boden 2012). Clozapine was particularly associated with major fetal malformations by a few large trials, although the causal link is not certain

(Gentile 2010). It is important to note that complications associated with pregnancy may be increased in women with schizophrenia and affective disorders (e.g. placental abruption) compared to the general population, according to a population based study (Jablensky 2005); thus it is difficult to ascertain whether the reproductive adversities and poor neonatal outcomesare due to the illness itself, medications, confounding factors or chance. Often patients are on a combination of medications, which hinders the identification of the causal agent.

Robakis and Williams 2013 interestingly advocated an algorithm to guide the choice of atypical psychotics in pregnancy from discussions with obstetricians and paediatricians, and suggested that safety rather than efficacy was emphasized in treating pregnant women (Robakis 2013). They also concluded that clinicians were more likely to choose antipsychotics which have worked well in the past, with continuous modification of treatment regimens and rigorous monitoring for adverse events (Robakis 2013). Indeed, many of the studies in our report demonstrated these principles; although ideally, clinicians should base clinical judgements on evidence-based-medicine, rather than clinical experience alone. FDA safety ratings have also been introduced in order to aid the decision making process.

Albeit largely unavoidable, our report is severely limited as it was mainly derived from sparse case reports and small population cohort studies/case-control series where available; there was no randomized controlled trial to-date. This has a few implications. Firstly, there is a huge potential for risk of bias; the lack of statistical analysis and multiple confounding factors mean that these results could be due to effects of chance and may not be extrapolated to the general population. Replicability of findings on larger high-quality prospective placebo-controlled studies with adequate statistical analyses is crucial to ensure the validity and reliability of these results. Secondly, there was a large degree of heterogeneity with no/little standardization of the degree and severity of illness, methodology, and outcome measures. The large variability within patient cohort hindered any valuable comparisons and conclusions to be made. Future studies could benefit from objective, standardized trials, with considerations for other factors including comorbidities, concomitant medications and timing of gestation. It is however understandably challenging to conduct rigorous research in this subgroup, given the ethical dilemmas involved. Nevertheless, some studies have used objective outcome measures, with the analysis of placental transfer of antipsychotics to confirm fetal exposure being one such example (Newport 2007). We also did not consider other pharmacological agents e.g. typical antipsychotics which were often included in trials/studies; nor did we perform detailed analyses on combination regimens. Future studies could also perhaps start to introduce newer atypical antipsychotics such as lurasidone and ziprasidone for consideration in this subgroup.

While there are severe ethical limitations to the amount and vigor of research that can be conducted on these women, we recommend clear documentation of all aspects of each patient's illness, and this good practice should start way before conception. Indeed, the management of psychiatric conditions is not limited to pharmacological therapy; psychological interventions, holistic and preventative medicine, with good professional working relationships play a substantial role. With advances in treatments, significantly higher numbers of women with mental illnesses are able to conceive until full term; and where the situation arises, lengthy discussions would need to take place between healthcare professionals and parents to include the risks of discontinuing or changing current medications versus the risks of adverse effects on the unborn child, benefits of therapeutic versus prophylactic interventions, issues around compliance, contraception, breastfeeding, and other modalities of support. Clear documentation and follow-up reviews are essential in order to better understand the impact of the illness on pregnancy, and monitor the efficacy and safety of pharmacological agents introduced.

To-date, no firm conclusions can be drawn regarding the use of atypical antipsychotics in pregnant women or women of childbearing age. Nonetheless, generally, atypical antipsychotics have better safety profiles in pregnancy compared to conventional pharmacological agents (mood stabilizers/typical antipsychotics) (Dodd 2006). Our study show that certain agents, particularly quetiapine may be beneficial and safe where indicated, although larger, randomized controlled trials with objective measures are warranted to add validity.

CONCLUSION

The pharmacological management of schizophrenia and bipolar disorder, and indeed mental health in women of childbearing age is highly complex, and requires a holistic approach in order to maximize both the maternal and child's physical and mental wellbeing. NICE CG192 focuses on prediction, support and general management for this group of service users in pre-, ante- and postnatal care, whilst allowing for flexibility in patients' preference. We present the current evidence on atypical antipsychotics for schizophrenia and/or bipolar disorder in pregnancy; and good management requires a solid understanding of the illnesses themselves and the pharmacodynamics of medications used. Although firm conclusions cannot be drawn at this stage, current studies have improved our understanding on the pharmacology and risk: benefit profile of these drugs, with each antipsychotic having varying efficacy and side-effects. Each treatment option should therefore be thoroughly discussed and the decision should be based on balancing the benefits and risks, with considerations for patient preference and other patient factors. There is also a strong emphasis on continuous monitoring and modulation of drugs in order to ascertain the best possible outcome for patients.

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