

# COMMON ADVERSE DRUG REACTIONS WITH PSYCHIATRIC MEDICATIONS AND AN APPROACH TO THEIR MANAGEMENT

*Adverse drug reactions are as important in psychiatric practice as they are in any other branch of medicine.*

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Adverse drug reactions are defined as an 'unexpected, unintended, undesired or excessive response to a drug',<sup>1,2</sup> which would include 'allergic reactions and idiosyncratic reactions that are an abnormal susceptibility to a drug peculiar to the individual'.<sup>1,2</sup> It is important to understand that psychiatric medications, as with medication generally (including non-prescription compounds, e.g. St John's Wort<sup>3</sup>), carry a risk of adverse reactions. For example, a major concern with St John's Wort is that of interactions with conventional drugs, including selective serotonin reuptake inhibitors, due to induction of the cytochrome P450 enzyme system.<sup>3</sup>

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A side-effect refers to an additional pharmacological effect of a medicine, which might be undesirable but might also be therapeutic – depending on the context. For example, anti-histaminergic agents (such as promethazine) can be used for their sedating side-effect rather than their primary intended effect in behaviourally disturbed psychiatric patients, usually together with an antipsychotic agent.<sup>4</sup>

## Range of agents

A MEDLINE search using the terms 'adverse drug reactions' (ADRs) and 'psychiatry' yielded 113 entries, implicating a wide range of psychiatric drugs in ADRs. Most of these papers were case reports, but there are in addition a range of ADR studies over a number of years that have reported on psychiatric patient samples.

In a recent study of ADRs among hospitalised psychiatric patients, the psychiatric drugs most commonly associated with adverse reactions were antipsychotics and mood stabilisers.<sup>1</sup> The antipsychotics in question were second-generation antipsychotics, e.g. olanzapine, and conventional antipsychotics, e.g. haloperidol. As expected, the spectrum of ADRs conformed to those typically associated with either group of drugs, i.e. second-generation psychotics were associated with metabolic ADRs and conventional antipsychotics with neurological ADRs. Of interest in the study, which was conducted over a 3-year period, is that non-psychiatric medications more frequently caused ADRs in this setting than did psychiatric drugs (51.6% v. 48.4%). The non-psychiatric drugs most frequently causing ADRs were cardiac and anti-epileptic agents. This highlights an important issue in the management of psychiatric patients, i.e. the extent to which medical co-morbidity exists with psychiatric illness.<sup>5,6</sup> Among the side-effects of antipsychotics, notably the second-generation antipsychotics, cardiometabolic side-effects feature prominently. Dyslipidaemias were associated with olanzapine and clozapine use, albeit less frequently.<sup>1</sup> Of interest in this study<sup>1</sup> is that the anti-epileptic agent associated with ADRs was phenytoin, which is not an agent typically used in psychiatric patients. Anti-epileptic agents are frequently used in psychiatric



patients for a range of indications, including seizure disorders co-morbid with or underlying psychopathology or as treatment for bipolar disorder. Earlier studies have generally reported that patients taking antipsychotics, with specific mention of both 'low potency' and 'atypical' antipsychotic drugs, most commonly experience ADRs.<sup>7-9</sup>

## Extent of the problem

The burden of ADRs in hospital is reported in a variety of ways in studies. ADRs were the cause of 10 per 1 000 patient days in a psychiatric hospital.<sup>9</sup> In two large long-term facilities where antipsychotic drugs were prescribed there were 9.8 ADRs per 100 resident months, with ADRs more likely to be associated with antipsychotic drugs than other drugs, with an odds ratio of 3.4.<sup>7</sup> ADRs were responsible for 0.3% of transfers from a psychiatric hospital to a medical facility.<sup>8</sup> A recent study identified 93 ADRs over a 3-year period in a state psychiatric hospital with an average daily patient population of 301.<sup>1</sup> Comparison between studies is difficult because of the different ways in which samples have been studied and data reported.<sup>9</sup>

A study of hospitalised psychiatric patients from German-speaking countries (Germany, Switzerland and Austria), the *Arzneimittelsicherheit in der Psychiatrie* (AMSP) Drug Safety Programme, provides comprehensive data on a range of ADRs. This study includes 35 sites and describes documented ADRs occurring between 1993 and 2000.<sup>10</sup> During this period a total of 122 562 inpatients were included, with 1 613 assessed as having experienced a 'severe' ADR (definition follows in next section) – giving an overall prevalence of 1.32%. The likelihood of having experienced a severe ADR was rated as 'possible, probable or definite', as opposed to 'questionable' (each category was defined). Of the 1 613 cases, 1 202 (74.5%) were judged to be probable or definitely drug related, with 1 132 falling into the probable category.

#### AMSP study

Given the comprehensive data collection related to ADRs it is worth considering the AMSP study in greater detail. This study provided data on severe adverse reactions experienced by psychiatric inpatients, with the intention of doing so within the context of routine clinical practice, therefore providing the information in a way that informed clinicians of a real-world setting, as opposed to that of a clinical trial. The aims of this study were not only to document the extent and range of such ADRs, but also to look at factors associated with their occurrence, e.g. drug interactions, and provide information related to management. The scope of content include ADRs related to antidepressants and neuroleptics and data on severe movement disorders, blood dyscrasias, cardiac complications, galactorrhoea and hyperglycaemia, therefore providing one of the most comprehensive data sets of ADRs related to psychiatric patients.<sup>10</sup> It should be noted that over the period of the study some 45 hospitals had participated at one or another time, with the nature of participating hospitals including both university- and non-university-affiliated hospitals and encompassing both acute and long-stay patients. The study was designed to be continuous and open ended, therefore providing, and continuing to provide, data reflecting the ADR status quo within the study sites.

The definition of ADRs in the AMSP study<sup>10</sup> differs from definitions noted earlier<sup>1,2</sup> in that an ADR is defined as 'any adverse event occurring at doses adequate for therapeutic or prophylactic treatment' and excludes 'intoxication or inefficiency'.<sup>10</sup> The definition does not really define 'adverse' as such, but does qualify the nature of the administered doses at which such a reaction is experienced. The AMSP study goes further by providing detail regarding what would constitute a severe ADR, not only in terms of broad parameters but also in terms of organs.

With regard to the former any reaction to a drug that is potentially life threatening, severely compromises health or functioning or necessitates transfer to another clinical discipline for management constitutes a severe ADR. Regarding the organ-specific criteria, these are somewhat extensive in terms of the range of organ systems for which such criteria are provided and therefore beyond the scope of this article, but as an illustration the criteria include the extent of liver enzyme changes and specific neutrophil counts that constitute such reactions of a hepatic or haematological nature. The study also includes specific clinical presentations regarded as severe ADRs within the so-called psychic and neurological systems. The former includes delirium and/or confusion, and the latter extra-pyramidal symptoms or seizures.<sup>10</sup>

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#### Nature of ADRs

The findings of the study were divided into ADRs associated with drugs and organ systems. In relation to drugs, antidepressants and antipsychotics were most frequently associated with ADRs, accounting for approximately 90% of all ADRs. With regard to organ systems, neurological adverse reactions, e.g. seizures, and psychiatric adverse reactions, e.g. toxic delirium, were most common and accounted for approximately 40% of all ADRs, with dermatological, cardiovascular, hepatic and haematological ADRs accounting for approximately 43%, and gastrointestinal, endocrine, urological, sexual, body weight and respiratory categories (in descending order of frequency) accounting for the balance.<sup>10</sup> The study yielded a range of articles related to the specific organ systems and drug classes published in the same supplement as the paper by Grohmann *et al.*,<sup>10</sup> that has served to provide a general description of the study and the findings. Most recently a paper emanating from the AMSP study, analysing suicidality as an adverse event associated with antidepressant use, was published, having reviewed data between 1993 and 2008, therefore emphasising the earlier intention of the study to be open ended and continuous.<sup>11</sup> Given the implications of such a clinical adverse event, a brief discussion of this study is pertinent.

#### Suicidality

The controversial nature of psychiatric drug prescribing is no better illustrated than in the furore that emerged around the possible implication of antidepressant drugs in the emergence of suicidal ideation and acts, thus constituting a severe ADR by any definition. In this regard the paper by Teicher *et al.*<sup>12</sup> sounded the alarm, and in so doing raised the issue of how readily behaviour associated with a given treatment is directly related to the treatment or reflects the ongoing development of a condition (in this instance major depression) while on treatment that is a function of the condition and not the treatment. A number of meta-analyses followed, with the general trend towards no direct association but with the understanding that the randomised controlled trials on which the meta-analyses were based may not in themselves be adequate to detect such associations for a host of methodological reasons.<sup>11</sup> In this AMSP study, 142 090 adult patients taking antidepressant medication between 1993 and 2008 in 54 psychiatric institutions were observed. A total of 33 instances of suicidality were reported (including suicidal ideation  $N=12$ , attempts  $N=18$ , and suicide completion  $N=3$ ). Of the 33 cases, 14 were deemed probably and 19 possibly related to the drug. Of the 33 cases, 23 were associated with restlessness, and it was noted that serotonin reuptake inhibitors and serotonin-noradrenaline reuptake inhibitors were most commonly associated with suicidality. Notwithstanding the findings, the conclusion was that antidepressants rarely lead to suicidality.<sup>11</sup> Such a finding has important implications for prescribers, patients and their families in terms of the absolute risk, which is low,

but critically in terms of which agents are most implicated and the nature of clinical presentation, suggesting the possibility of suicidality. In essence, the data provide information that informs management.

### Management

Management begins with awareness of potential for ADRs, not only in terms of psychiatric drugs being prescribed but also in terms of co-prescribing of psychiatric and non-psychiatric drugs, together with an appreciation of the physical status of the patient in terms of the current physical examination and of documented medical conditions. A number of psychiatric drugs require pre-commencement blood screening, of which lithium and clozapine represent two specific examples, with renal and thyroid screening for the former and haematological screening for the latter. In addition, there is a need for routine and ongoing monitoring while prescribing either drug, together with checking of lithium levels (which is also required for drugs such as sodium valproate). In essence, prevention through appropriate screening and monitoring is optimal. Such an approach informs current thinking in relation to the metabolic syndrome and the prescribing of second-generation

antipsychotics, with an increasing awareness and emphasis within the discipline of the extent to which sufferers from severe mental illness are disadvantaged in terms of access to and receiving appropriate and necessary medical, non-psychiatric care.<sup>13</sup>

### Conclusion

The burden of ADRs with the use of psychiatric drugs varies among studies. This may in part be due to different study methods. The most convincing data appear to be from the AMSP study, with a prevalence of 1.3%.<sup>10</sup> The range of implicated agents is diverse but antidepressant and antipsychotic drugs are most commonly associated with ADRs. Regarding organ systems, it would appear that most are affected, but with a preponderance of ADRs of a neurological or psychiatric nature. The ability to ascribe causation with absolute certainty remains problematic in many instances, but erring on the side of caution – without being alarmist – is probably advisable. While the relative risk of an ADR is low, the implication of such an event for an individual patient is potentially life threatening. Clinicians need to be aware of the potential for ADRs as the first step in management.

References available at [www.cmej.org.za](http://www.cmej.org.za)

## IN A NUTSHELL

- ADRs are associated with a range of psychiatric drugs.
- Few studies exist, although there are many case reports involving ADRs among psychiatric patients.
- The studies tend to report data differently, making comparisons difficult.
- The AMSP study provides the most comprehensive data, documenting a rate of 1.32 % for ADRs among hospitalised psychiatric patients.
- Antidepressants and antipsychotic drugs are most commonly associated with ADRs.
- Second-generation antipsychotics, e.g. olanzapine, are typically associated with metabolic ADRs, and first-generation antipsychotics, e.g. haloperidol, with neurological ADRs.
- The absolute risk for suicidality associated with antidepressant use is low.