

## PSYCHOTROPIC PRESCRIBING IN HIV

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The use of psychiatric medication in patients with HIV infection is a complex area, but given the high rates of psychiatric disorder in this population – possibly as high as 50%<sup>1</sup> – it deserves further consideration. A number of issues need to be thought about, including the nature of both the psychiatric illness and the HIV infection, the use of antiretroviral therapy (ART), and patient-related factors.

### PSYCHIATRIC ILLNESS IN HIV

The interaction between HIV infection and psychiatric illness is complex, with many authors suggesting that psychiatric disorders in HIV-positive individuals are frequently under-recognised and under-treated.<sup>2,3</sup> It is well established that there is an increase in the prevalence of a number of psychiatric disorders in HIV-infected individuals, internationally<sup>4,5</sup> and in South Africa.<sup>6,7</sup> There may also be changes in the clinical picture in patients with psychiatric disorders after HIV infection<sup>8</sup> and an interactive effect between HIV infection and vulnerability to psychiatric illness.<sup>9</sup>

### ANTIRETROVIRAL THERAPY (ART)

In patients on ART who may require psychotropic medication important considerations include possible side-effects of existing antiretroviral medications, as well as potential interactions between ART and psychotropics. Psychosis, mania, agitation and suicidal ideation have all been associated with ART. The antiretroviral agents most commonly implicated include abacavir, efavirenz and nevirapine.<sup>10</sup> Although in most cases it would appear that the psychiatric adverse effects occurred shortly after initiation of the antiretroviral agent, cases occurring over a year after commencement have also been reported.

Drug interactions between ART and psychotropic medication, as well as with other medications the patient may be receiving, is another area that must be approached with some caution. A number of psychotropic agents that are potent enzyme inducers are contraindicated for use with almost all antiretroviral agents as they can seriously compromise antiretroviral therapy; these include carbamazepine, phenytoin, primidone and St John's wort. Caution is also advised when using certain selective serotonin re-uptake inhibitors (SSRIs) and benzodiazepines (see below).

With regard to the antiretrovirals, a wide range of interactions with psychotropic agents have been described, and careful observation in the first weeks to months

after any change of these medications is required. All the protease inhibitors, as well as the non-nucleoside reverse transcriptase inhibitors, are metabolised by the cytochrome P450 system and may therefore possess enzyme-inducing or inhibiting properties. In the South African setting, the commonly used agents that require the most caution are efavirenz, which may induce or inhibit CYP3A4, and nevirapine, which may induce CYP3A4. Many other antiretrovirals have been reported as interacting with psychotropics, and a more comprehensive list of interactions can be obtained at the HIV InSite Database of Antiretroviral Drug Interactions (<http://www.hivinsite.com/><sup>11</sup>).<sup>10</sup>

### PATIENT-RELATED ISSUES

It is also critical to take into account a wide range of psychosocial factors that may adversely affect the individual patient's willingness and capacity to take medication correctly and for the required duration.

- Many HIV-positive patients may already be on complex drug regimens.
- Patients are often going through a complex process of adjustment to and acceptance of a lifelong diagnosis of HIV/AIDS with associated stigmatisation.
- Many of these patients will be suffering from some degree of cognitive impairment.
- In many psychiatric disorders, particularly those associated with psychosis, insight may be lacking or may fluctuate.

When these issues are considered in their entirety, it becomes clear that the importance of selecting the simplest possible regimens, the provision of regular psycho-education and counselling, and the recruitment of family members or others as treatment partners for all the medications the patient may be receiving cannot be emphasised too strongly.

### PSYCHOTROPIC USE IN SPECIFIC DISORDERS

While this review is based as far as possible on the existing evidence base for psychotropic medication use in

HIV/AIDS, it is important to note that empirical evidence is limited in many instances. Data often come from studies outside sub-Saharan Africa, and in turn the applicability of such evidence to South African populations may require interrogation.

### ANXIETY DISORDERS

The vast majority of the existing literature on the treatment of these disorders in HIV-positive patients describes the use of psychotherapeutic approaches rather than medication. As an initial approach, this is perhaps appropriate in general populations.

Benzodiazepines have been shown to provide rapid symptomatic relief from acute anxiety states, but they should be used with caution in post-traumatic stress disorder (PTSD) and panic disorders, and they have severe limitations in terms of their capacity to produce tolerance and dependence.<sup>12</sup> There is no reason to believe that the situation differs in HIV. Further caution must be applied with the use of alprazolam, midazolam and triazolam, which are dependent on CYP3A4 for metabolism, so that inhibitors of this enzyme system may increase the half-life of these drugs, possibly causing over-sedation and respiratory depression. Additionally, CYP3A4 inducers may lower serum levels and reduce the effect of these drugs.<sup>13</sup> Perhaps safer choices are benzodiazepines such as oxazepam, lorazepam, and temazepam, which are metabolised by glucuronidation.<sup>3</sup> However, a cautious approach is required in all cases, with careful titration of initial doses and observation for accumulation.

There is some evidence in support of buspirone as an anxiolytic in HIV-positive individuals, as reported in two small studies.<sup>14,15</sup> However there are also reports of dyskinesias, myoclonus, psychosis and mania in HIV-positive patients.

Lastly, and perhaps of most clinical relevance, it should be noted that the SSRIs are widely recommended as first-line treatment for a variety of anxiety disorders, including PTSD, generalised anxiety disorder (GAD), panic disorder and obsessive-compulsive disorder in the general population.<sup>10</sup> There is little evidence to suggest this is not the case in HIV-infected individuals, and the use of these drugs is discussed below. In using the SSRIs to treat anxiety disorders it is useful to initiate medication at smaller doses than is usual for the treatment of depression, and in some cases the brief use of small doses of benzodiazepines during the initial period may be helpful.

Alternative hypnotics, such as zopiclone and zolpidem, should be used with caution as interactions with CYP3A4 have been reported. Beta-blockers are sometimes used in the treatment of GAD, but in the context of HIV, consideration must be given to the possibility of respiratory disorders and peripheral neuropathies, in which case these agents are best avoided.

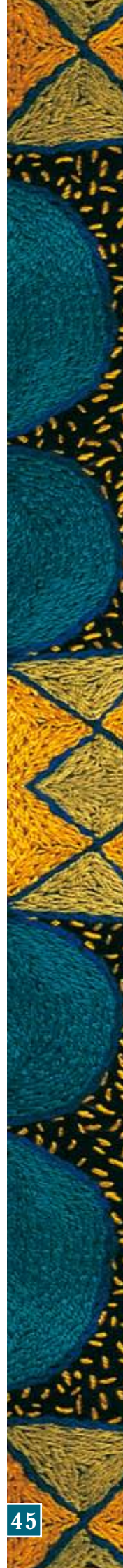
### DEPRESSION

Depressive disorders and their treatment in HIV-positive populations have received far more attention than other psychiatric disorders. A particular area of concern has been raised by studies indicating poor adherence to ART regimens<sup>16</sup> and increased morbidity<sup>17</sup> in HIV-positive patients with untreated depression. Despite this, a systematic review and meta-analysis of controlled trials to examine efficacy of antidepressant treatment among HIV-positive depressed individuals<sup>18</sup> identified only seven studies, almost all of which involved white males in First-World populations. Of these, only three (involving fluoxetine, paroxetine and imipramine) reported significant effects.

Looking more broadly at the literature on tricyclic antidepressants (TCAs), there is evidence to suggest that response rates are similar to those in HIV-negative populations<sup>19</sup> and that these agents are as effective as SSRIs in depressed HIV-positive patients.<sup>20</sup> It would therefore seem that TCAs are an appropriate choice in this context. It is, however, important to consider a number of issues relating to the side-effects of these drugs, particularly anticholinergic effects (which may lead to dry mucous membranes and an increased vulnerability to mucocutaneous candidiasis), alpha-adrenergic blockade (which can result in problematic postural hypotension, particularly in patients with neuropathies and other systemic illnesses), and prolongation of the QTc interval. Other issues such as the potential for sedation and weight gain may be problematic or beneficial, depending on the particular circumstances.

With regard to the SSRIs, although the best evidence for efficacy to date favours fluoxetine and paroxetine, these agents are potentially problematic in conjunction with ART (in particular nevirapine and ritonavir) as both are metabolised by CYP2D6, while fluoxetine also inhibits CYP3A4; there is therefore an increased risk of serotonin syndrome, as well as of changes in levels of antiretrovirals. Although the quality of evidence for the efficacy of both citalopram and sertraline in HIV-positive populations is less compelling, some evidence does exist<sup>21,22</sup> and there is little to suggest interaction with CYP2D6 or CYP3A4. Possible side-effects that may be of concern with this class of drugs include gastro-intestinal disturbances and increased anxiety. These can, however, be mitigated by initiating therapy with low doses and slowly increasing to therapeutic levels.

There is weak evidence to support the efficacy of newer-generation antidepressants in treating depression in HIV-infected patients.<sup>23</sup> Mirtazapine has minimal effect on CYP2D6 or CYP3A4 and has proved a popular choice because of its relatively sedating effects and tendency to improve appetite and promote weight gain.<sup>3</sup> There is currently little evidence on the use of venlafaxine and duloxetine in depressed HIV-positive patients,





and metabolism by CYP2D6 and inhibition of this system would argue against their use as a first-line treatment. Bupropion has been studied in one open trial for depression in HIV-positive patients and was found to be effective,<sup>22</sup> but there are concerns that efavirenz, ritonavir and nelfinavir may increase levels by inhibiting bupropion hydroxylation.<sup>3</sup>

A number of alternative agents for the treatment of depression have been studied quite extensively in HIV. Concerns have been expressed about potential interactions between St John's wort and various antiretrovirals,<sup>24</sup> so this is best avoided. Testosterone may be of use in men with hypogonadism, which may occur as a result of HIV infection,<sup>25</sup> but is not broadly effective as an antidepressant. With regard to psychostimulants, their potential side-effect profile, which includes psychosis, mania, weight loss, anxiety, insomnia and cognitive deficits, would mitigate against their use as first-choice agents.

Finally, the use of electroconvulsive therapy should not be overlooked in cases of treatment resistance or where medication has not been tolerated. Although not well studied in HIV, there are reports of its beneficial use<sup>26,27</sup> and it should not be refused simply on the basis of HIV status.

#### BIPOLAR DISORDER AND MANIA

Manic episodes, either as part of bipolar disorder or as a secondary complication of HIV infection,<sup>5,28</sup> are well described in HIV. In a first manic episode it may be preferable to avoid the immediate use of a mood stabiliser in favour of an antipsychotic (see 'Psychosis', below), with short-term use of benzodiazepines (see 'Anxiety Disorders', above) if necessary. In established bipolar disorder, recurrent or relapsing secondary mania, or where this initial approach has proven inadequate, the use of mood stabilisers is indicated. In bipolar mania the preferred first-line mood stabilisers are lithium and sodium valproate, with carbamazepine as a second choice.<sup>10</sup> As mentioned earlier, however, the potent enzyme induction attributed to carbamazepine makes it a poor choice in HIV.

There are mixed reports on the use of lithium in HIV-positive patients. Concerns have been expressed regarding possible increased sensitivity to side-effects<sup>29</sup> and worsening of cognitive impairment;<sup>30</sup> however, a recent study<sup>31</sup> demonstrated quite the opposite, with improvements in HIV-associated neurocognitive impairment on lithium. This may be related to its capacity, together with sodium valproate, for the inhibition of glycogen synthase kinase 3 beta (GSK-3 beta), a survival-regulating enzyme.<sup>32,33</sup> Lithium is excreted unchanged in the urine, so interactions with ART are unlikely. Its narrow therapeutic index, however, is of some concern, particularly when diarrhoea is likely, and extreme caution is required with medications that may reduce the glomerular filtration rate. It can therefore be concluded that lithium

may be a reasonable choice, provided that it is well tolerated on initiation and that excellent compliance can be guaranteed.

Valproate (available as sodium valproate or valproic acid) is generally considered to be better tolerated than lithium and safer with regard to therapeutic index, but neutropenia, hepatic failure and the potential for teratogenesis in women of child-bearing age remain a concern.<sup>10</sup> Its potential to inhibit CYP3A4 may result in interactions with some antiretrovirals, and caution is advised when using it in combination with nevirapine and efavirenz. It has also been shown to inhibit GSK-3 beta.<sup>33</sup> Early reports raised some concerns that it may increase viral loads by stimulating replication.<sup>34</sup> More recently it was suggested that this effect, in combination with ART, may lead to the possibility of cure by depleting latent viral stores,<sup>35</sup> but unfortunately this has not been substantiated.<sup>36</sup> Whether sodium valproate may lead to cognitive decline in HIV-positive individuals or not is not entirely resolved, however, with some studies showing no decline<sup>37,38</sup> but one study suggesting problems with longer-term use at higher doses.<sup>39</sup> This concern is supported by a fairly extensive literature pointing to adverse neurocognitive effects of valproate in individuals with cognitive impairment, although it should be noted that valproate is not unique in this effect either (e.g. Gualtieri and Johnson<sup>40</sup>). While valproate is therefore probably a reasonable choice of mood stabiliser in this setting, it would seem prudent to exercise caution with higher doses and to monitor cognitive function carefully, shortly after initiation as well as in the longer term.

#### PSYCHOSIS

The older 'classic' antipsychotics, haloperidol in particular, have been shown to be safe and effective in studies of HIV-infected patients with schizophrenia<sup>8</sup> as well as those with HIV-associated psychotic disorder.<sup>41,42</sup> However, these patient groups have increased susceptibility to extrapyramidal side-effects (EPSE) and possibly to tardive dyskinesia (TD) and neuroleptic malignant syndrome.<sup>10</sup> Although chlorpromazine may be less likely to produce EPSE and is helpful in restless patients when benzodiazepines are not well tolerated, this is similarly limited to a lower dosage range. Further problems include the well-established side-effects of neutropenia, alpha-adrenergic blockade and anticholinergic effects. It can therefore be concluded that these agents may be useful and, where psychosis or delirium with psychotic symptoms are present, a trial, at initial doses of not more than 1 mg of haloperidol, or the equivalent, is indicated; at higher doses, EPSE can be expected. It is also worth noting that an *adequate* trial of any anti-psychotic requires at least a week of treatment at any dosage increment, if not longer.

Given the high risk of EPSE and TD, the newer, second-generation or 'atypical' antipsychotics may be a

reasonable first-line approach, and are clearly a rational second line when EPSE have become apparent. Theoretically, at least, an additional advantage of these agents is their high potency as serotonin 5HT<sub>2A</sub> receptor antagonists, which may be a useful effect as pro-phylaxis against, and treatment of, progressive multifocal leukoencephalopathy.<sup>43</sup> Risperidone was shown to be effective in the treatment of HIV-associated psychotic and manic symptoms in one series of 17 cases,<sup>44</sup> where a particularly good response in patients with manic symptoms was noted. EPSE can however be a problem, even in low doses,<sup>45</sup> and severe complications as a result of interactions with ritonavir have been described.<sup>46</sup> There is very little literature of substance on the use of other second-generation agents, other than for short-term, symptomatic use in delirium. Some care must be taken with olanzapine, owing to metabolism by CYP2D6 (the same may be said of clozapine), but the low risk of EPSE and growing evidence of their efficacy as mood stabilisers<sup>10</sup> make these agents compelling choices. The use of clozapine may be considered in HIV-positive patients with treatment-resistant schizophrenia, but given this drug's association with neutropenia it is best used as a last resort in settings where CD4 counts remain high and white cell counts can be closely monitored.

### DELIRIUM

As mentioned at the outset, the most critical step in managing delirium in the setting of HIV infection is to vigorously identify and treat possible causes (see the article on assessment and treatment of psychosis in HIV-infected individuals in this issue). The short-term use of low-dose antipsychotics and/or benzodiazepines may be considered if clinically indicated to manage behavioural disturbance.

### HIV-ASSOCIATED DEMENTIA

As described elsewhere in this issue, the mainstay of treatment of HIV-associated dementia is ART, but short-term, symptomatic use of antipsychotics and mood stabilisers may be helpful.

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