

# Management of Chronic Psychotic Ambulatory Outpatients

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The introduction of novel atypical antipsychotic medicines has raised new possibilities in the treatment of psychotic patients. In particular, the discovery of pharmacologic agents that may ameliorate the most stubborn positive and also negative symptoms without adding the burden of major side effects is revolutionizing treatment expectations. However, it is also becoming abundantly clear that successful treatment requires more than just the administration of a medicine. Treatment must also address the inner experiences of the patient, as well as the social and psychological handicaps that are associated with the illness. Some of the relatively neglected complications of using typical antipsychotic medicines include hyperprolactinemia and antipsychotics that may require concomitant treatment with anticholinergic agents, which themselves have an array of side effects. This article presents a detailed method for deciding when and how to use the new medications effectively and how to manage the transition from one medicine to another. (*J Clin Psychiatry 1998;59[suppl 19]:30-35*)

We are currently witnessing a revolution both in our understanding of the psychoses and of the methods that we can employ to treat them. First amongst the new treatments are the new antipsychotic agents. Much has already been made of the data supporting their clinical efficacy, and we are now at a stage where we have gained a considerable amount of clinical experience in their use and have a better idea of how to integrate the pharmacologic and nonpharmacologic components of the management of patients with psychoses. Since there are still many issues in the practical management of psychotic patients that are the subject of ongoing research, I shall, in the course of this article, make clear which recommendations are based upon research and which upon practical experience.

It is evident that the psychotic illnesses can destroy the lives of sufferers and their families, but we sometimes fail to sufficiently examine what it is about the symptoms and their sequelae that leads to this horrendous destruction of people's abilities to function domestically and in society. These shall be reexamined in terms of positive and negative symptoms, disturbances of mood, neurocognitive decline, and impairment of social intelligence. Finally, the

sometimes neglected issues of secondary and tertiary handicaps following from psychotic illnesses will be revisited. Improvements in the understanding of the management of the psychoses mean that treatment goals can become more ambitious. The modern management of the psychoses is now less restricted than it was in the past (Table 1).

A useful notion when looking at the deficits of patients with psychotic illness is that of social intelligence. This is a concept modified from one used in the study of mental handicaps. The reason for concentrating upon the idea is that the components of social intelligence constitute a neurologic system,<sup>1</sup> which is preferentially affected in schizophrenia (Table 2). Data from a number of sources have buttressed the notion that the psychoses in general, and schizophrenia in particular, may be associated with cortical lesions, which may even be of greater importance than changes in medial temporal lobe structures.<sup>2</sup>

## FOUR-VECTOR TREATMENT MODEL

It is also important to consider the various dimensions of the illness, and to treat all 4 vectors of illness simultaneously: (1) biological, (2) social, (3) psychological, and (4) spiritual (Figure 1).

### Biological Treatment

The mainstay of biological treatment of the psychoses remains antipsychotic medications. The first of the conventional antipsychotics—chlorpromazine—was introduced in 1952, and these agents have undoubtedly helped huge numbers of patients. They are inexpensive and often effective, while the newer agents cost considerably more

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**Table 1. The Central Postulates of the Modern Management of Psychosis**

The modern management of psychosis is no longer just the management of positive symptoms, excitement, and dyscontrol. The modern management of psychosis has to consist of more than just prescribing a medicine, however good that medicine may be.

**Table 2. Social Intelligence**

Social intelligence is a notion taken and modified from the mental handicap literature. It encompasses the repertoire of responses that humans have developed in order to function as social beings. These include:

- Social distance
- Ability to recognize and to generate facial expression
- Self-awareness
- Cleanliness (possibly)

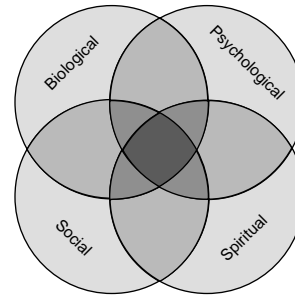
and still have less of a track record. Thus, 6 important questions must be addressed:

1. What is the role of conventional oral antipsychotic agents?
2. What are the indications for using atypical antipsychotics?
3. How should the practitioner choose between different atypical antipsychotics?
4. How should the transition between agents be managed clinically?
5. What is the role of decanoate preparations?
6. Are the newer antipsychotic medications actually substantially more expensive?

Although conventional antipsychotics have served well for so many years, one of the main problems of these agents has always been that they have an array of unpleasant side effects, in addition to variable and currently unpredictable efficacy profiles. The main advantages of using them have been familiarity and cost. However, as suggested above, clinicians should now be raising their ambitions in the management of the psychoses, and aiming for more than simply controlling positive symptoms, excitement, and disorganization, and conventional agents are woefully inadequate in treating any more than these symptoms. That being said, there are undoubtedly many patients who have done well on conventional antipsychotics for many years, and it would simply be meddlesome to change their regimen. In addition, some patients—particularly those who are particularly concrete in their thinking—become anxious about any change in their routine, and for them it may also be best to continue with conventional agents. However, many clinicians have found it sobering to learn that a high proportion of outpatients simply stopped complaining about residual psychotic symptoms or side effects with conventional antipsychotics. Yet they would discuss these matters when specifically probed, and some have become grateful that physicians

**Figure 1. Four-Vector Model of Treatment**

Patient's illnesses are conceptualized to have a number of dimensions, and treatment is targeted on each of the following components:



have shown concern about these matters and tried treatment with the newer agents. Finally, in the acute setting some patients do need the higher degree of sedation afforded by the older agents, but this is rarely a problem in the outpatient setting.

The key reasons for using an atypical antipsychotic are lack of efficacy of conventional agents on either positive or negative symptoms; unacceptable side effects—particularly extrapyramidal and endocrine (vide infra), particularly if concomitant treatment with anticholinergic agents is needed; and first-episode patients. The choice of which atypical antipsychotic to use is still difficult, although the publication of the first study comparing risperidone and olanzapine<sup>3</sup> tends to favor the latter. More studies are currently underway, which, when published, will aid clinicians in making the choice. A method for managing the transition to the newer agents is discussed below.

Clearly some patients still do best on decanoate preparations. After all, most are on decanoate therapy for a good reason: lack of compliance. However, there may be reasons for considering atypical agents in some patients on decanoate treatment. There is anecdotal evidence about patients who will comply with an atypical when they would not previously take conventional oral agents. Clearly the possibility of a change from a decanoate must be weighed carefully in each individual patient, and if undertaken, must be done very cautiously because of the real risk of precipitating a relapse. Finally, some patients on decanoate preparations have prominent negative symptoms, which have been helped by the addition of an atypical agent, although this is contravention of the normal practice of trying to use only one antipsychotic agent at a time. Clearly, this is a field in which further research is needed.

Atypical antipsychotic agents are considerably more expensive than the older agents. However, there are persuasive pharmacoeconomic data to indicate that certainly for clozapine,<sup>4</sup> and perhaps also for olanzapine, the overall

cost of the medicine is offset by a reduction in hospitalization and social handicap.

### **Social Treatment**

When considering the social treatment of the psychoses, it is valuable to target each of the handicaps that afflict sufferers. The first is the *primary handicap*, which arises as a direct consequence of the illness itself, and takes the form of the positive and negative symptoms. Negative symptoms are characterized by underactivity and a generalized slowness, social withdrawal, poverty of speech, flat affect, lack of initiative, and poor motivation. It has been known since the pioneering work of Wing and Morris<sup>5</sup> that in chronically institutionalized patients, there is a high correlation between the severity of negative symptoms and low levels of social stimulation. On the other hand, excessive stimulation can lead to the reemergence of positive psychotic symptoms. *Secondary handicaps* occur as a result of being ill, but are not a direct product of the illness itself. These are the consequences of, for instance, institutionalization, social avoidance, withdrawal and decline, and the consequences of having to take those medications that are associated with major extrapyramidal and hormonal side effects. *Tertiary handicaps* are the social disabilities which follow from the illness: stigma, restricted social networks, poverty, unemployment, and isolation. These tend to persist over time.

Social treatment is designed to help deal with the secondary and tertiary deficits, to help reintegration by, for example, teaching or re-teaching social skills, and finally by improving confidence. It was shown as long ago as 1959 that ambulatory male patients with schizophrenia did worse after discharge if they had a lot of contact with their families.<sup>6</sup> This led to the development of the concept of "expressed emotion" (EE) in a family, which is a composite of both the form and content of speech. The most important aspects of EE for the person with schizophrenia are critical comments and overinvolvement. Family intervention studies<sup>7,8</sup> have shown that a reduction of high EE can reduce the rates of relapse in schizophrenia. These methods are particularly effective when compared with antipsychotic medications.<sup>7,8</sup> Given that these studies were performed by using agents with an array of unpleasant side effects that militated against continued compliance, it is to be expected that a combination of family intervention strategies with atypical antipsychotics may be even more effective.

### **Psychological Management**

There is ample evidence that psychological treatment is associated with an improvement in the control of psychotic illnesses. The aim is to help the patient deal with the consequences of the illness, to optimize performance, and to help the family deal with the illness and the sufferer. This is achieved by counseling and supportive psycho-

therapy. In addition, personal, family, and group psychoeducation about the illness, triggers to relapse, and expressed emotion are often useful.

### **Spiritual Management**

People's spiritual beliefs are not usually considered in the management of psychotic illness, but they really ought to be, not least because most patients feel them to be an important part of their nature. In addition, there is a high frequency of religious themes in abnormal belief systems. Clearly there is no place for mental health workers to force beliefs upon patients and their families, but rather the intention is to respect their belief systems. An additional point is that many areas of the country have a dearth of community support programs for the mentally ill, but sometimes churches, temples, and other religious organizations can offer a tremendous amount of support for both the person with a major mental illness and their families.

## **OBSTACLES TO COMPLIANCE**

Now that a framework for the treatment of the psychotic patient has been established, the problems need to be examined, i.e., what stands in the way of patients participating in this sort of treatment plan? One of the central problems in the management of psychotic patients is compliance with a treatment regimen. (It has recently been suggested that the term *compliance* should be replaced with the less paternalistic term *concordance*.<sup>9</sup>) The first major hurdle to be overcome is that of insight: the understanding that the patient has an illness needing treatment.<sup>10</sup> The next is that of the unacceptable side effects of medications, particularly with the conventional antipsychotics. The best known of these is the extrapyramidal side effects. However, it is becoming more widely recognized that there is another major group of side effects, which have been largely neglected in the past: those resulting from elevations of the hormone prolactin.

### **Hyperprolactinemia**

While the neurologic effects are relatively easy to see, and patients and their families have no qualms about complaining about these problems, the effects on prolactin may be far more occult. Although hyperprolactinemia in association with antipsychotic medications was first described in 1974,<sup>11</sup> it has been largely neglected by the psychiatric community. However, in a recent reanalysis of all the published data on the association between hyperprolactinemia and antipsychotic medications found in a MEDLINE search, it transpired that the levels of prolactin seen are frequently within the ranges found with prolactinomas, which are known to produce multiple endocrine disturbances. Patients are less likely to complain about the sexual side effects of medications, and health care professionals are notoriously reluctant to ask about

them. For a long time, hyperprolactinemia appeared to be inevitable with antipsychotic medicines, and perhaps it was not important to enquire about potential consequences of hyperprolactinemia. However, now that the new antipsychotic medicines—olanzapine, quetiapine, and clozapine—produce only minimal or transient elevations of prolactin, it is important to establish whether patients are suffering from these side effects, which would be an indication for a change in the type of agent being used.

In women, hyperprolactinemia results in amenorrhoea and the cessation of normal cyclic ovarian function. However, some hyperprolactinemic women are not amenorrhoeic but have irregular menstrual cycles, menorrhagia, or, less often, may have normal cycles, but are infertile. This is most likely due to a defect in luteal function. Galactorrhoea occurs in about 30% to 90% of women with hyperprolactinemia, and may also occur in males.<sup>12</sup> Women may also experience other symptoms of estrogen deficiency, such as vaginal dryness during intercourse and loss of libido. About 5% of women with hyperprolactinemia complain of hirsutism as well as menstrual disturbances. Obesity has also been associated with hyperprolactinemia, and may improve when patients are treated with bromocriptine, which, together with amantadine, has been suggested as a potential treatment for drug-induced hyperprolactinemia.<sup>13</sup> Naturally it is preferable to select an antipsychotic agent that does not elevate prolactin levels and obviates the need for such polypharmacy. One potential psychiatric consequence of hyperprolactinemia is that in some women, amenorrhoea has undergone delusional elaboration, with the development of a false belief about being pregnant. The author has seen a patient who consequently attempted to “deliver” the delusional pregnancy with a knife.

In men, hyperprolactinemia is associated with erectile impotence, hypospermatogenesis, and loss of libido. As in women, this is mediated by the central effects of prolactin: testosterone levels are low, and the hypogonadism is associated with abnormal regulation of gonadotrophins. Hyperprolactinemia produced by pituitary tumors or acromegaly can be correlated with erectile impotence, which tends to improve as levels of prolactin fall, either as the underlying problem is treated or bromocriptine is used. A fall in prolactin is associated with a rise in plasma testosterone, so it is not clear whether the effects are due to prolactin itself or are secondary due to the effects of prolactin on testicular function. A recent study<sup>14</sup> has indicated that erectile impotence is a common cause of noncompliance with antipsychotic medications. Galactorrhoea may rarely also occur in males, and again has, in the author's experience, led to delusional elaboration.

Apart from the sexual complications of hyperprolactinemia, attention has recently been focused on the longer term effects of this hormonal imbalance. Some breast cancers are stimulated by prolactin and the possibility that

drug-induced hyperprolactinemia could generate or exacerbate tumor has been a considerable concern. The question of an association between different cancers and schizophrenia has been studied since the early part of this century and more intensively since the discovery that typical antipsychotics may be associated with hyperprolactinemia. The data so far seem to indicate that there is no excess of breast cancer in treated women,<sup>15,16</sup> although at least one study has found a significant increase in breast cancer.<sup>17</sup> The worry is that at the time of earlier studies, women had had less exposure to antipsychotics—and the attendant risk of hyperprolactinemia—than currently, when there are many women who have been using these agents throughout their adult lives and are now in higher risk groups for breast cancer. A recent mammographic study of chronic psychiatric patients found an incidence of diagnosed breast cancer that was 3.5 times higher than that for women in a general hospital setting, and 9.5 times higher than that reported in the general population.<sup>18</sup> This study had some methodological problems but does indicate the urgent need for further research in this field.

A further potential complication of hyperprolactinemia is a reduction in bone mineral density, perhaps leading to frank osteoporosis, since there is a well-recognized negative association between serum prolactin levels and bone density.<sup>19</sup> This is of particular importance in chronic psychiatric patients, who may also have other risk factors for the development of osteoporosis, such as smoking, dietary deficiencies, and a sedentary life style.<sup>20,21</sup> On the other hand, obesity may have some protective effect against the development of osteoporosis. Bone loss may also occur in men, and the degree of bone loss in men is related not so much to absolute prolactin levels, but rather to the duration of hyperprolactinemia.<sup>22</sup>

In the past, there were a number of unsuccessful attempts to find correlations between clinical response to antipsychotics and a rise in plasma prolactin.<sup>23</sup> However, it was discovered that some of the most effective antipsychotics, in particular clozapine,<sup>24</sup> olanzapine,<sup>25,26</sup> and quetiapine,<sup>27–29</sup> are not associated with a significant rise in prolactin levels. Sertindole and ziprasidone are also not associated with a significant rise in prolactin levels, although risperidone may be associated with an increase in prolactin levels.<sup>30</sup> Indeed, it appears that risperidone may increase prolactin levels to a greater degree than haloperidol and also to cause sexual dysfunction in both men and women.<sup>31</sup> Although some have attempted to minimize the importance of hyperprolactinemia in psychiatric practice, it is clearly a significant cause of psychological and physical morbidity.

## ANTICHOLINERGIC MEDICATIONS

An additional problem that needs to be faced when making the decision concerning which antipsychotic

**Table 3. Unwanted Effects of Anticholinergic Medications**

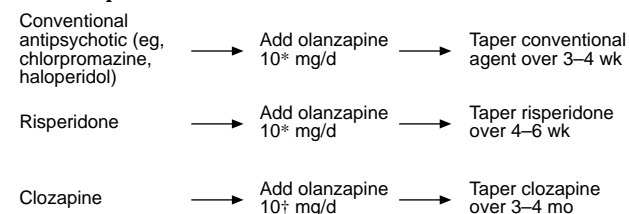
Dry mouth, blurred vision, urinary retention, and constipation
Unmasking or exacerbation of tardive dyskinesia
Toxic confusional state ("atropine psychosis")
Abuse potential because of mild euphoriant effects
Exacerbation of "positive" symptoms of schizophrenia
Adverse effect on learning and memory
Reduced action of conventional antipsychotics by inducing hepatic enzymes

medicine to use is whether it might become necessary to use anticholinergic medicines to deal with unwanted side effects, in particular extrapyramidal side effects. There are three contraindications to the use of anticholinergic medicines: glaucoma, prostatic hypertrophy, and tardive dyskinesia. Furthermore, it is sometimes not appreciated that anticholinergics have themselves an array of significant side effects. These are summarized in Table 3.

The direct effects from anticholinergics' action on peripheral cholinergic receptors—i.e., dry mouth, urinary retention—are familiar to all prescribers. However, some additional problems may not be as familiar to clinicians. Many of us will have seen patients—usually elderly—who have developed toxic confusional states through the use of these agents, and it is also not uncommon to see patients who have been abusing them for their mild euphoriant effects. In many urban areas, there is, in fact, a small black market in anticholinergic medicines. The exacerbation of positive symptoms by anticholinergics was first described by Johnstone and colleagues in 1983,<sup>32</sup> and this has been not only a robust finding, but one that is often an unappreciated factor in the management of psychotic patients, in whom it is easy for a vicious cycle to develop. First, the anticholinergics exacerbate positive symptoms, which leads to an increased dosage of antipsychotic that requires more anticholinergics, and so on. Thus, it is clear that it is always wise to avoid anticholinergic medications if at all possible, and the most direct way of doing so is to use those antipsychotics with few if any extrapyramidal side effects: namely, olanzapine, quetiapine, and, in special situations, clozapine. Risperidone tends to have few extrapyramidal side effects at very low doses, but in most patients they will emerge rapidly as the dosage is increased.

### Managing the Transition to Atypical Agents

Several authors have presented methods for switching patients from conventional or even atypical agents to other atypicals, and a consensus is emerging on the best and safest way to do this. However, we must emphasize that what is presented here, and what has become known as the "Philadelphia method," is based upon a deep knowledge of the pharmacology of these various agents together with a very large amount of clinical experience in executing these changes, rather than a series of formal clinical studies. The major virtue of this method is its simplicity. The disadvantage is that it is not individualized. A major prob-

**Figure 2. Managing the Transition From Other Antipsychotics to Olanzapine**

\*Reduce the dosage of olanzapine in the elderly, or if the patient is medically ill.

†May start at 20 mg/day if patient previously maintained on high doses of clozapine.

lem with discontinuation of most antipsychotics is that patients may develop a poorly understood "withdrawal syndrome," so that they not only become as psychotic as before, but sometimes the psychosis is exacerbated. In addition, different antipsychotics act at different receptor sites and perhaps even in different parts of the brain.

Thus, it is crucial that any changes in medication are completed very cautiously (Figure 2). The key points are that the transitions must be done very slowly. When olanzapine was first available, the author saw a number of patients being treated with clozapine, in whom the drug was stopped abruptly before olanzapine was introduced. The outcome was invariably disastrous.

### CONCLUSION

We are learning a great deal about how to use the new medicines, as well as understanding more about the mechanisms underlying the psychoses. It has to be emphasized that the treatment of the psychoses has to be a multidimensional undertaking, which aims to treat all aspects of the illness. While acknowledging that many patients will unfortunately not respond to treatment, we also need to be ever more ambitious in our treatment goals. Our patients and their families have waited a long time for treatments that might improve the quality of their life and allow the sufferer to reconnect with his or her family and with society.

*Drug names:* amantadine (Symmetrel), bromocriptine (Parlodel), chlorpromazine (Thorazine and others), clozapine (Clozaril), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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#### DISCLOSURE OF OFF-LABEL USAGE

The author of this article has determined that, to the best of his clinical estimation, no investigational or off-label information about pharmaceutical agents has been presented that is outside Food and Drug Administration–approved labeling.