Conventional Antipsychotic Prescription in Unipolar Depression, I: An Audit and Recommendations for Practice

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Background: Despite narrow indications for conventional antipsychotics in depression, recent reports confirm a suspicion that they are widely prescribed in nonpsychotic depressive conditions.

Method: Data from the case notes of over 510 patients with unipolar depression (unvalidated clinical diagnoses) were collected between June 1997 and January 1998 from community and acute units in 1 National Health Service (NHS) Trust. The aim of this audit was to assess the extent and pattern of antipsychotic prescription in this sample.

Results: More than a quarter (N = 138) of the sample (N = 494) were currently prescribed an antipsychotic; 40% of these received an antipsychotic without any recognized indication. The mean time on antipsychotic therapy was 3 years. Patients on antipsychotic therapy were, on average, taking twice as many total medications as those not on antipsychotic therapy. Patients with psychotic depression were taking an average of nearly twice the antipsychotic dose of nonpsychotic patients.

Conclusion: Current clinical guidelines commend careful antidepressant choice in preference to polypharmacy. A number of drug choices for specific depressive presentations are summarized from recent sources.

(J Clin Psychiatry 2003;64:568–574)

Received March 18, 2002; accepted Sept. 11, 2002. From the Department of Psychiatry, the University of Hull, Willerby, United Kingdom (Dr. Mortimer and Mr. Tyson); and the Department of Psychology, New School for Social Research, New York, N.Y. (Mr. Wheeler Vega).

The authors report no financial or other relationship relevant to the subject matter of this article.

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Traditionally, antipsychotic drugs were indicated in affective disorders complicated by psychosis, such as unipolar psychotic depression, bipolar psychotic depression, and mixed affective states.[1] Such practice was founded on studies that demonstrated increased efficacy of an antidepressant/antipsychotic combination in psychotic or treatment-resistant depression, over antidepressant monotherapy.[2–5] However, this evidence may be somewhat limited[6,7] and is not entirely consistent.[8–10] The inconsistencies may be attributed to the lack of modern diagnostic criteria for depression in the earlier studies.[11] Results from samples including significant numbers of patients with mixed affective disorder, personality disorder, or schizophrenia may be misleading, since antipsychotics may have a valid role in reducing depressive symptoms in such patients. Furthermore, conventional antipsychotics have been reported to induce depressive symptoms when used in treatment of bipolar disorder.[12–15] Overall, there is no clear evidence of the utility of conventional antipsychotic treatment in unipolar or bipolar depression without psychotic symptoms.

The latest British National Formulary[16] limits antipsychotic use in depressive disorder to treat the behavioral disturbance in agitated depression and to alleviate severe anxiety in the short term. Indeed, depression is given as a "caution" regarding antipsychotics. Within influential recent guidelines on psychotropic prescribing in depression,[17] mention of antipsychotics is limited to 2 atypical drugs in resistant patients in the following terms: "may be worth trying, but little published support." Our own review[2] challenged the antidepressant/antipsychotic combination as first-line treatment for psychotic major depression.

There has been little published research on the use of antipsychotics in the treatment of nonpsychotic affective disorders (Table 1). One recent article, a drug-monitoring study of the use of a selective serotonin reuptake inhibitor (SSRI) antidepressant in Germany,[18] revealed that psychiatric comedication was relatively commonplace. The authors collected demographic and prescription information on 2817 patients prescribed paroxetine. At least 70 patients (2.5% of the total sample) not classified as delusional, schizophrenic, or schizoaffective were reportedly prescribed antipsychotics during the drug-monitoring period.

Table 1. Studies of Antipsychotic Prescription in Depression

	Patients Taking an Antipsychotic		Patients Taking a Redundant Antipsychotic		Mean Chlorpromazine Equivalents (mg/d)	
Study	N	%	N	%	Psychotic	Nonpsychotic
Zaninelli and Meister (1997)[18]	230	9.5	70	2.5	N/A	N/A
Wernicke et al (1997)[19]	36 approx	0.9	36 approx	0.9	N/A	N/A
Parker et al (1991)[20]	8	23	6	17	156	88
This audit	138	28	55	11	175	96

Another large study[19] looked at the prescription of concomitant medications in 25 randomized, double-blind, controlled trials (RCTs) comparing fluoxetine with a tricyclic antidepressant (TCA) or placebo. Of the 4016 patients with major depression included in the meta-analysis, 0.9% were coprescribed an antipsychotic and, among these, significantly more patients were taking fluoxetine (1.4%) than a TCA (0.4%). The authors suggested that this may indicate the use of antipsychotics as sedatives in agitated patients—fluoxetine being relatively more agitating than TCAs. As patients with psychotic illness were excluded from the analysis, all the antipsychotics (for approximately 36 patients) can be considered redundantly prescribed. This meta-analysis of clinical-trials data cannot be taken to represent ordinary clinical prescribing practices; the very low prescription of concomitant antipsychotics may instead reflect the RCT context.

An earlier study[20] compared the medications prescribed to a sample of 35 psychotic, and 35 matched nonpsychotic, depressed patients. Among the findings was that a similar proportion of psychotic (23%) and matched nonpsychotic (17%) patients were prescribed an antipsychotic as part of their treatment. There was a significant difference in dosages; psychotic patients received roughly double the chlorpromazine "equivalents" of the nonpsychotic group.

A concern that the use of antipsychotics in nonpsychotic depression was relatively frequent in everyday clinical practice within the Hull and Holderness Community Trust (health care provider organization) prompted an audit of antipsychotic prescription in unipolar affective disorders. The aims of this audit were:

- To evaluate the extent of prescription of antipsychotics in unipolar affective disorders.
- To assess those patients prescribed antipsychotics without clear indications and to change their medication when it could be rationalized.

This article reports the first stage of this process. The second stage is reported in an accompanying article.[21]

METHOD

The first phase of this Trust-wide audit involved recording the prescription of all psychiatric medications to inpatients and outpatients with primary unipolar affective disorders. Patients' files were to be inspected until either 500 had been ascertained or all inpatient and community records had been examined. The data collection and literature search were carried out between June 1997 and January 1998. Patients with depression as a secondary diagnosis to schizophrenia, bipolar disorder, or schizoaffective disorder were excluded.

Hull and Holderness Community Trust patient information systems do not currently provide diagnostic information; consequently, patients' notes were hand searched at inpatient and outpatient units. Generally, clear formal diagnoses were unavailable (ICD-10 diagnoses were found in only 35 case notes). Thus, inclusion of patients in the audit was often made on less than ideal information, i.e., the clinical diagnosis of the patients' consultants (attending physicians in psychiatry).

Five hundred ten patients were ascertained from all inpatient units in the Hull and Holderness Community Trust, and from 5 of the 6 community units. Patients fell under the care of 6 consultants.

The following categories of data were collected for all patients with depression as a primary or comorbid diagnosis: name, age, sex, date of birth, responsible consultant, date of audit, ICD diagnosis, informal clinical diagnosis from psychiatrist's letters, and all current psychiatric medications with dose and frequency. For patients described as having a psychotic depression, prescribed an antipsychotic, or both, data in the following categories were also collected: date of onset of psychotic symptoms if noted, start of antipsychotic treatment if noted, presence of psychotic symptoms at onset or currently (delusions, hallucinations, psychomotor agitation, or retardation), and any noted unwanted effects.

RESULTS

The key results are summarized in Figure 1. Of the 510 cases ascertained, 494 were sufficiently complete for inclusion in the data analysis. Women appeared significantly more frequently (290 women, 204 men; $\chi^2 = 14.6$, $p = .0001$). This sex difference reflects the accepted population distribution of affective disorders.[22] Patients' age ranged from 18 to 75 years, with a mean of 44 years. There was no association between age and sex within the total group.

Antipsychotic Prescription

Of the 494 patients, 138 (28%) were currently prescribed at least 1 antipsychotic medication. This percentage (28%) is higher than in previous studies (Table 1) with (non-significantly) more women (N = 83) than men (N = 55) in this subgroup. There were no age or sex differences between those (N = 138) prescribed an antipsychotic and those not (N = 356). Seven patients were prescribed an atypical antipsychotic, olanzapine (5%).

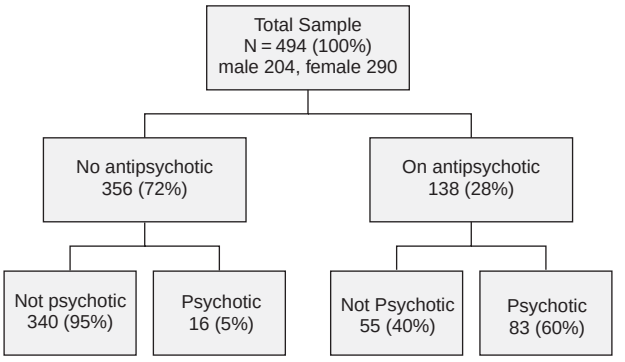
Of those 138 patients prescribed an antipsychotic, 83 (47 women, 36 men) had a diagnosis of psychotic depression (N = 59) and/or noted psychotic symptoms (N = 71). These patients will be referred to as the psychotic group. A formal or clinical diagnosis of psychotic depression included descriptions such as depressive episode or recurrent depression with psychotic symptoms, depressive psychosis, delusional depression, paranoid depression, affective illness with psychotic features, and agitated depression. Descriptions of 4 symptoms widely considered indicative of psychotic depression, delusions, hallucinations, and psychomotor disturbance (agitation or retardation), were construed as evidence of psychosis, with or without a stated clinical diagnosis of psychotic depression.[23]

The other 55 of 138 patients prescribed an antipsychotic (36 women, 19 men; 11% of the total sample, 40% of those so prescribed) had neither an appropriate diagnosis (diagnosis that warranted an antipsychotic), nor mention of psychotic symptoms either previously or currently. These 55 patients will be referred to as the nonpsychotic group. There was no difference in age or sex between psychotic and nonpsychotic patients. No patient in the nonpsychotic group was prescribed olanzapine; all were taking conventional antipsychotics. Of those 356 patients not prescribed an antipsychotic, 340 were defined as not psychotic; the remaining 16 (5%) did fulfill the criteria for psychotic depression.

Psychotropic Polypharmacy

For all groups, the total number of prescribed medications ranged from 1 to 6 (Figure 2). Neither age nor sex was related to the total number of medications prescribed. However, those 138 patients prescribed antipsychotics received overall significantly more medications than those patients who did not. One-way ANOVA revealed a highly significant variation ($F = 124.7$, $p < .0001$) between those 356 not prescribed an antipsychotic, those 83 prescribed an antipsychotic with some warrant, and those 55 without apparent indications for an antipsychotic. Given the strong positive skew of the data for the 356 not prescribed an antipsychotic, and the unequal group sizes, a more conservative nonparametric test (Kruskal-Wallis) was also performed, which confirmed the difference ($\chi^2 = 190.002$, $p < .0001$). The mean number of medications for the 356-patient nonantipsychotic group was 1.31 (SD 0.62); the means for the 2 antipsychotic groups were nonsignificantly different: 2.59 (SD 1.15) for the psychotic group and 2.47 (SD 1.00) for the nonpsychotic group. Whereas among those 356 nonantipsychotic patients only 14 (4%) were taking 3 or more medications, among those 138 antipsychotic patients, 57 (41%) were taking 3 or more medications.

Figure 1. Outline of Audit Data in 494 Patients With Unipolar Depression[a]



[a]Percentages for each sample are derived from the sample immediately above.

Antipsychotic Dosages

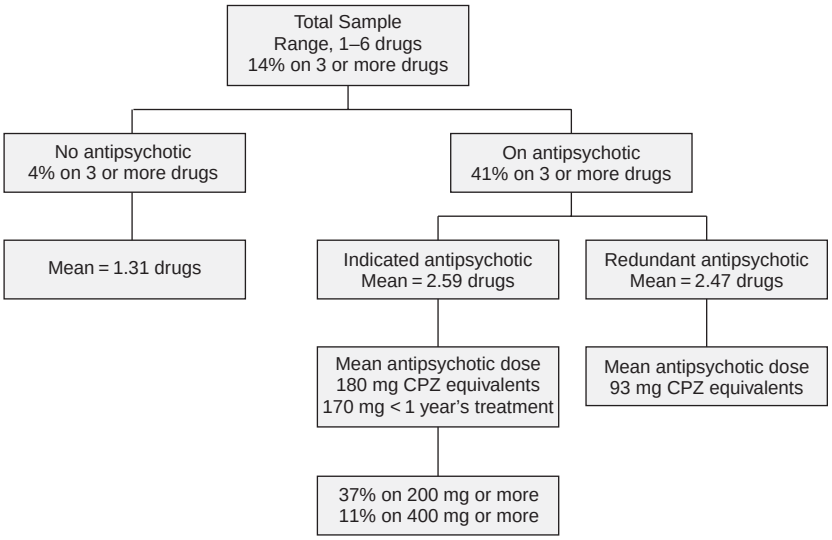
Antipsychotic dosages were converted into chlorpromazine equivalents by reference to the British National Formulary and consensus guidelines.[16,24] The mean dose for the psychotic group was 180 mg/day (SD 156; range, 10–750 mg/day). The mean dose for the nonpsychotic group was 93 mg/day (SD 96; range, 20–600 mg/day). This difference was statistically significant (independent samples 2-tailed t test = 3.84, $p < .001$).

In the psychotic group, 37% were on 200 mg/day or above; 200 mg/day was the median dosage prescribed (16 cases). Only 11% were on 400 mg/day or above. Twenty-four of the psychotic group had been treated with an antipsychotic for less than 1 year; the mean daily dose was 170 mg/day.

Duration of Antipsychotic Treatment
Vis-à-Vis Diagnosis

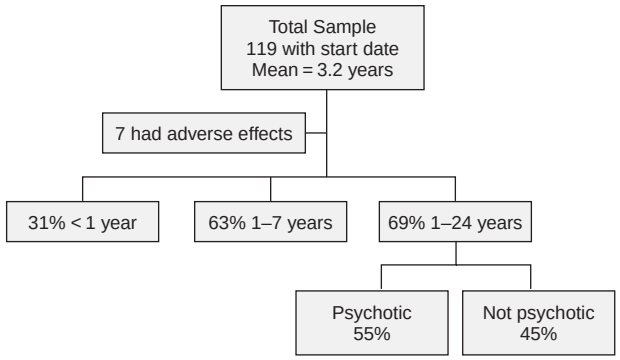
The start date of antipsychotic treatment, to the nearest year, was recorded for 119 patients; in the remaining 19 cases, no start date was found (Figure 3). The mean length of antipsychotic treatment was 3.2 years (SD 4.29); 37 cases (31%) were treated for less than 1 year. Seventy-five patients (63%) had been treated with antipsychotics for between 1 and 7 years, and 82 (69%) were treated for between 1 and 24 years. Of those 82 cases, 45 (55%) were classified as psychotic, and 37 (45%) as not psychotic.

Figure 2. Polypharmacy and Dosage of Antipsychotic in 494 Patients With Unipolar Depression



Abbreviation: CPZ = chlorpromazine.

Figure 3. Duration of Antipsychotic Treatment and Adverse Effects



Adverse Effects

Seven patients were noted as suffering unwanted (adverse) effects from their medications; all had been on antipsychotics for at least 1 year.

Prescription and Consultant

Two consultants of the 6 practicing at the time of the audit were responsible for 55% of the patients (270 of 494 patients). They were responsible for a greater proportion than this of the patients prescribed apparently redundant antipsychotics: 66% (41 of 55 patients). However, these consultants were also responsible for exactly the same percentage of psychotic patients who were appropriately prescribed antipsychotics: 66% (55 of 83 patients).

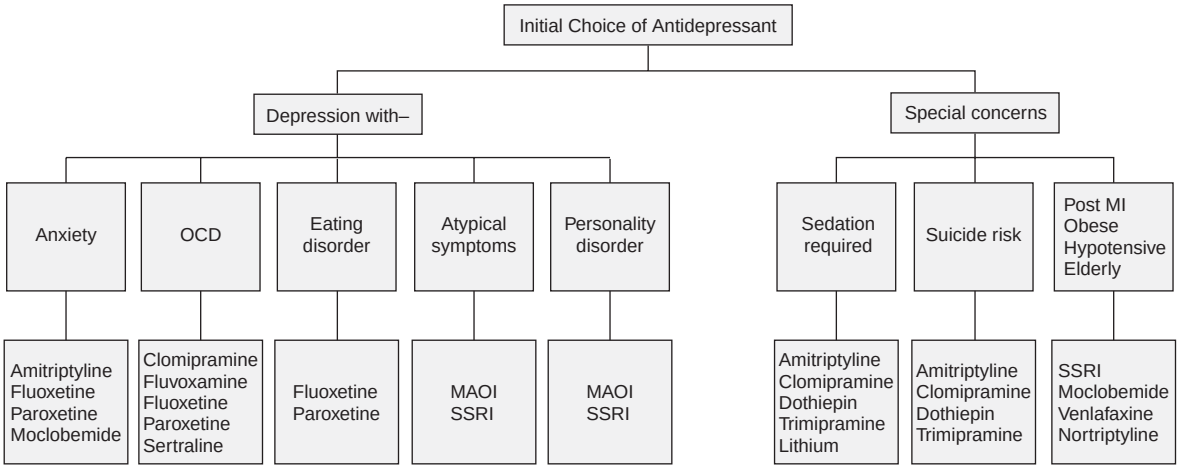
DISCUSSION

The outstanding finding of this audit was that 40% of patients with clinically diagnosed depressive disorders who were prescribed an antipsychotic received this treatment without any apparent clinical justification. Compared to earlier studies,[18–20] this is not the highest percentage of apparently unwarranted antipsychotic prescription as a proportion of the total, but is, perhaps, most representative of ordinary practice. Parker et al.[20] had a much smaller selected sample; Zaninelli and Meister[18] were monitoring the prescription of 1 relatively novel antidepressant and other drugs prescribed with it; and Wernicke et al.[19] were considering clinical trials, not everyday clinical practice.

It cannot be ruled out that, as was the case with early studies, this sample contained patients with bipolar disorder, personality disorder, or even schizophrenia, which would indicate the prescription of an antipsychotic. It was not possible to validate consultants' clinical diagnoses and exclude comorbidity by interviewing all the patients, but only to render this less likely by careful scrutiny of the case notes. Also, data on onset and duration of treatment were incomplete and may be conservative, and data on chronicity and other indicators of severity were not collected. However, our further study of 40 patients apparently prescribed a redundant antipsychotic[21] included independent scrutiny of the case notes by 2 clinicians; an interview with each patient, although not utilizing any diagnostic procedures, attempted to clarify outstanding diagnostic issues. In none of these patients was the original consultant's clinical diagnosis rescinded. It is possible that the consultants were prescribing intuitively for some patients, i.e., trying antipsychotic treatment because they had a feeling it would help given their previous experience with similar cases. This highlights the importance for senior medical staff to firm up the diagnostic formulation of individual patients, and, thus, afford some clarity regarding their psychotropic decision-making.

Antipsychotic prescribing for secondary comorbid depression in the context of failure to recognize or document the primary diagnosis would be consistent (although we believe unlikely) with the finding that use of an antipsychotic in both psychotic and nonpsychotic groups was associated with a vulnerability to polypharmacy. There is little justification for polypharmacy in the 40% without psychosis, however, in the absence of evidence that their illnesses were more severe. Polypharmacy imposes an

Figure 4. Choice of Antidepressant



increasing likelihood of drug side effects and interactions as well as possibly compromising adherence.

The dosage difference between psychotic and nonpsychotic patients closely matches what Parker et al.[20] (Table 1) found in their smaller sample, i.e., psychotic patients received nearly twice the dose prescribed to nonpsychotic patients. This implies the use of these drugs in the nonpsychotic group for problems other than psychosis, which are not felt to require such vigorous treatment, at least in terms of dose. Such problems may not amount to formal comorbid diagnoses. There are circumstances in which there is a tradition of (but no evidence base for) using a small dose of an antipsychotic: initial insomnia, mild anxiety. Once again, the notion that antipsychotics could have been prescribed intuitively (and perhaps not entirely appropriately) is supported.

In this audit and the previous study by Parker et al.,[20] average dosages for those diagnosed with psychotic depression were relatively low—under 200 mg/day chlorpromazine equivalents. Some authors[8,25] have noted that chlorpromazine equivalent dosages of 400 mg/day should be standard for psychotic depression, up to 1000 mg/day where necessary. Long-term maintenance dosages are commonly lower than acute medication dosages; only 4 acute patients, all with diagnoses of psychotic depression, were included in this audit. However, the closeness of the dose of patients treated for less than a year to the overall average (170 mg vs. 176–187mg/day) suggests that antipsychotic dosages for the psychotic group were fairly low early on in treatment and remained so. This is on the one hand desirable, given an imperative to avoid unnecessarily high doses and their attendant adverse effects. On the other hand, high doses have been recommended early on in treatment for swift resolution of symptoms[8,25] prior to tapering for maintenance.

It is of some interest that 45% of patients prescribed an antipsychotic for more than a year (39 of 82) had no diagnostic or symptomatic indication. This is not entirely inconsistent with acute use of antipsychotics for night sedation in these situations. Such persistent prescribing may simply reflect that doctors are more motivated to add medications than to risk discontinuing them. The low reporting of adverse effects may well be an underestimate, attributable to failure to ask about and examine for side effects; alternatively, it may reflect the low doses used in the whole sample overall.

The variation in prescribing practice between consultants suggests some influence of personal factors—habit—on prescription. The pair of consultants responsible for 66% of apparently inappropriate prescribing were both fully trained specialists; the other 4 were either long-term locums with insufficient training for appointment to a substantive position or consultants practicing outside the specialty of general adult psychiatry. There is a severe chronic shortage of fully trained general adult psychiatrists in the United Kingdom. It is likely that the 2 substantive general adult specialists were taking on numerous patients from the other practices in order to relieve the burden on their colleagues, and possible that these patients were perceived as more difficult, hence, the treatment decisions presented here.

How Do These Findings Accord With Accepted Wisdom on Prescribing for Patients With Unipolar Depression?

A semiformal British guide, the *Maudsley Prescribing Guidelines*,[17] suggests algorithms for treating a number of disorders, including unipolar depression, and provides useful profiles of antidepressants by class. Standard treatment consists of successively trying 3 antidepressants,

in adequate dosage and for an adequate length of time, from 3 separate classes. The older American Psychiatric Association's *Practice Guideline for Major Depressive Disorder in Adults*[22] offers some general prescription advice, based on clinical effectiveness, for particular depressive presentations. Figure 4 summarizes recommendations for a number of different presentations. It is more heuristic in terms of clinical utility than an evidence-based algorithm.

In both guidelines, the emphasis is on careful choice of a single drug, where possible, based on its known effects and the particular therapeutic action required. This point about the treatment of depression should be widely communicated; choice of an appropriate antidepressant should help to reduce troublesome polypharmacy. The serious adverse effects of antipsychotics, such as tardive dyskinesia, are well known and may be particularly likely in patients with affective disorders, even after short-term use.[26] In a recent review of combination and augmentation strategies in depression,[27] antipsychotics are not mentioned, with the exception of risperidone.[10] Nelson[27] points out that the disadvantages of polypharmacy may outweigh its advantages in many patients; however, one strategy is to tail off the second drug once remission has been achieved. This was possible in 50% of patients treated with add-on lithium[28] and 50% of elderly patients treated with add-on lithium, an antipsychotic, or SSRI.[29] When the failure rate and the success rate are equal (50%), it is difficult to make a decision to change medication, or not.

Polypharmacy in itself may not necessarily be uniformly undesirable. Multiple therapies for single diagnoses have a long and honorable history in other areas of medicine. It is generally the case that more severe illnesses require to be treated from more than 1 pharmacologic perspective. If the goal of treatment for depression is remission of illness as opposed to symptomatic response,[30] then polypharmacy may well be justified, at least in the short-to-medium term. Such patients need review, and the possibilities of poor compliance, side effects, and drug interactions must be borne in mind.

There is indeed evidence for an increasing use of polypharmacotherapy in refractory mood disorder.[31] Despite similar degrees of recovery, the mean number of discharge medications doubled from 1.5 in 1974–1979, to 3.0 in 1990–1995. Strikingly, the percentage of patients discharged on more than 3 medications escalated from 3.3% to 43.8% over the same period.[31] This work took place in a tertiary, research-oriented referral center for treatment-resistant patients, most of whom were bipolar. It seems likely that many were on antipsychotic therapy. A similar figure, 41%, of antipsychotic-treated patients in our sample were on 3 or more medications, despite not being just discharged, treatment resistant, or bipolar.

It was suggested[31] that the reasons for the increase in polypharmacy observed could include the referral of more severe patients to the service, owing to more intensive previous treatment efforts in the community, the recognition and referral of more early rapid-cycling patients, or an increasing severity of affective disorder in the general population (possibly accounted for by genetic anticipation). With the exception of the last possibility, none of these causes can be applied to our subjects, who were unselected.

A further possibility for increasing polypharmacy suggested by these authors[31] is the increasing number of clinical treatments available. The advent of atypical antipsychotics has led to some attempts to revisit the issue of antipsychotics in diagnoses without schizophrenia, including depression.[7] Indeed, some preclinical evidence suggests that atypical drugs may be effective in animal models of depression,[32] that there is commonality between clozapine and antidepressants in effects on the GABA receptor system,[33] and that a polymorphism of a serotonin receptor (which may be acted upon by both antidepressant and atypical antipsychotic drugs) is associated with both affective disorder and schizophrenia.[34] Clinical studies of atypical antipsychotics as single or add-on therapy are generally positive in psychotic depression,[4,6,35–37] nonpsychotic depression,[10] treatment-resistant illness,[26] and mixed samples.[5,38-40] Furthermore, atypical antipsychotics in studies of acute mania appear not to precipitate a switch into depression, unlike the experience with conventional antipsychotics.[41–43] Although one must be wary of the commercial aspects of marketing, in which a new drug is accompanied by new indications or inflated prevalence of the old ones, it would seem that not all antipsychotics are the same. This particularly regards the lack of marked depressogenic effects of atypical drugs. Even allowing that the antidepressant benefits of atypical drugs need further evidence before they can be considered proven, by contrast, there has never been any evidence that conventional antipsychotics have antidepressant effects at all.

Clinical Implications

The clinical implications include the following:

- Low-dose, long-term conventional antipsychotics seem relatively popular in unipolar depression without psychotic indications.
- The rationale for antipsychotic treatment should be clearly recorded.
- Careful choice of antidepressant may generally obviate the need for adjunctive antipsychotics in nonpsychotic depression.

Drug names: amitriptyline (Elavil, Endep, and others), chlorpromazine (Sonazine, Thorazine, and others), clomipramine (Anafranil and others), clozapine (Clozaril and others), fluoxetine (Prozac, and others), fluvoxamine (Luvox and others), nortriptyline (Aventyl, Pamelor, and others), olanzapine (Zyprexa), paroxetine (Paxil), risperidone (Risperdal), sertraline (Zoloft), trimipramine (Surmontil), venlafaxine (Effexor).

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