The Case for an Individual Approach to the Treatment of Depression

David Healy, M.D., F.R.C.Psych.

Early reports of the discovery of antidepressants in the 1950s have remained as little-known findings. Had the discovery of isoniazid, an agent with no clear action on monoamine systems, and that of reserpine, which depletes monoamines, been more widely known, then the monoamine lesion theories of depression, as proposed by Schildkraut in 1965, may not have been written. If the lesion in depression is lowered brain monoamine levels, then antidepressant agents that increase monoamine levels should work for all patients. If this were the case, optimizing treatment effect sizes with a minimum of side effects and some demonstrable specificity to depressive disorders would be possible. This is not the profile of antidepressants in clinical practice. Alternatively, if antidepressants act on constitutional types to provide appropriate therapeutical principles, then the efficacy would stem from an ability to suppress symptoms and to elicit or maintain conditions that allow recovery in a subgroup of patients who would otherwise remain nonresponsive. Current monoamine selective antidepressant principles embody “get-up-and-go” (noradrenergic) and emotional reactivity-reducing (serotonergic) principles. Different antidepressants are, therefore, likely to have different treatment effect sizes in different constitutional types. A further important aspect of antidepressant selectivity will lie in the extent to which these agents promote a sense of well-being during the maintenance phase of treatment.

The story of antidepressants did indeed begin with the treatment of tubercular patients with hydrazide derivatives and the observation by orthopedic surgeons of concomitant mood-elevating effects. In one sense, the discoveries were all but inevitable. However, there were 2 hydrazides in use at the time—isoniazid and iproniazid—and the first efforts to treat exclusively depressed patients were not with iproniazid in 1957, but rather with isoniazid in 1952. The physician involved was Lurie, who went on to treat a range of depressed patients with isoniazid. He found this drug to be extremely effective—so much so that he and his coworker Salzer conducted 2 studies. Whereas Kline’s first claims were made on the basis of 7 patients and Kuhn’s discovery of imipramine was based on dramatic responses from 3 or 4 patients, Lurie and Salzer reported on a total of 86 patients, of whom two thirds responded within 2 or 3 weeks of starting treatment. These data from Lurie and Salzer were much more convincing than the data from either Kline or Kuhn 5 years later. This discovery by Salzer and Lurie of isoniazid’s antidepressant effects was confirmed in 1952, when Buisson, working in Paris with Delay, also reported on the antidepressant properties of isoniazid. The replication of Lurie and Salzer’s data is important in that isoniazid is not an MAOI and, therefore, does not act by simply increasing monoamines in any of the conventional ways. In addition, it is worth noting that other non-MAOI hydrazides, such as cynarizide, were in use in the...
mid-1950s for their possible antidepressant effects, and these also appeared effective. Finally, in addition to the discovery of an antidepressant, Lurie also coined the word antidepressant, and he used it 10 years before anyone else. In contrast, Kline referred to his own discovery as a “psychic energizer,” while Kuhn saw his as a “thymoleptic.”

A second discovery of an antidepressant took place 2 to 3 years before either Kuhn’s or Kline’s discoveries. A drug had been developed that was associated with reports that it seemed to make people “better than well.” This led Wilkins to state in 1954 that “I have told many psychiatrists and others interested in psychotherapy that *Rauvolfia* is good psychotherapy in pill form.” Today, these are the kind of reports that would lead people to speculate that the drug must have been fluoxetine. The drug was, however, reserpine. Using reserpine, Davies and Shephard conducted the first prospective placebo-controlled, parallel-group, randomized trial in psychiatry. The trial was carried out in anxious and depressed patients, and the results showed that reserpine was an antidepressant.

The fact that reserpine, an antipsychotic so useful in the treatment of depression is, clinically, no surprise. All clinicians use antipsychotics in the management of mood disorders. Most antipsychotics have been shown in clinical trials to be useful in the treatment of depressive disorders. Reserpine, as an antipsychotic, might be expected on this basis to have a similar effect. Indeed, many antipsychotics are still used in this way. Flupenthixol, for instance, has been one of the most widely prescribed antipsychotics in Europe, with a great many of these prescriptions coming from primary care physicians and others who have prescribed it for its antidepressant properties.

In 1961, Klein and Fink randomly assigned 150 patients to treatment with chlorpromazine, imipramine, or placebo at the Hillside Hospital in New York. They found a clear response to chlorpromazine among patients with schizophrenia, but also an equally clear response to it among patients who were depressed. Imipramine, in contrast, did not make people with schizophrenia well. It seemed to be most useful in people who were phobic. This trial was repeated by Klein in a further 150 patients. In total, 300 people were randomized, one of the largest and most compelling trials in the history of psychiatry.

Chlorpromazine is an antidepressant, but most clinicians would not use it or other antipsychotics regularly to treat people with depression because, while these agents will improve the core features of the illness and may be necessary in the management of some patients, they will not restore the average depressed patient to a state of well-being. The quality of life that the recovered patient will have on continued antipsychotic treatment is not the quality of life we want people who are depressed to have when they have recovered from depression.

Taking all these elements into account, it is clear that if the full history of the treatment of depression in the 10 years before the catecholamine theory had been produced, an amine lesion theory of depression would not have been supported. In fact, a close reading of the title of Schildkraut’s seminal 1965 article reveals that it was written as “a review of supporting evidence.” At the brink of the millennium, it is clear that Schildkraut’s formulations regarding the action of antidepressants on monoamine systems remain correct. However, we need to look again at how such actions produce beneficial effects in the affective disorders.

**THE ADVENT OF THE SSRIs**

One of the hazards of holding to an amine lesion theory is that people are led to a view that all antidepressants work via a common mechanism and that at some point they converge on a common site of action. It is easy to see why, during the 1960s, people thought this could be the case. A look at the most commonly used antidepressants available at that time, and in the absence of any detailed biochemical knowledge of what these agents do, shows a group of drugs that literally look like keys to the same lock (Figure 1).

Despite this, a number of people were certain that not all these drugs were keys to the same lock. Kielholz, in Basel, Switzerland, produced a schematic outline of how antidepressants made depressed people well. This outline was founded on his clinical impressions. Kielholz claimed that some antidepressants acted more by enhancing drive whereas others acted more by affecting cognition.

Reviewing just such a schema for differential antidepressant effects, Carlsson suggested that those agents that were drive enhancing, according to Kielholz, were preferentially active on the catecholamine system, while those that were mood elevating had effects on the serotonergic (5-HT) system. It was this observation that led to the development of the selective serotonin reuptake inhibitors (SSRIs). In 1978, 10 years before the majority of SSRIs were introduced, indalpine was approved for clinical use in France. The first SSRI to be patented was zimelidine, in 1971.

With the benefit of hindsight, it is now possible to see that the various tricyclics can be classified in terms of their biochemical effects, and they are, respectively, serotonin-norepinephrine reuptake inhibitors (SNRIs; e.g., imipramine), norepinephrine reuptake inhibitors (NRIs; e.g., desipramine), SSRIs (e.g., clomipramine), and noradrenergic and specific serotonergic antagonists (NaSSAs; e.g., trimipramine). However, it should be noted that the so-called “serotonergic” TCAs (e.g., clomipramine) have active metabolites that are considerably more active on the noradrenergic system (e.g., desmethylclomipramine). Opipramol, which was widely used throughout central Europe in the 1970s and 1980s for mixed anxiety-affective
disorders, has minimal actions on any monoamine systems, but has actions on sigma receptors. So, these drugs are clearly not keys to the same lock. In fact, tianeptine, available in France as an antidepressant, increases rather than inhibits serotonin reuptake. Taking all these examples into consideration, it is clear that it is not possible to correlate the effects of these drugs on amine levels per se and their antidepressant effects. But, if the question “What do these drugs do functionally?” is asked, then the story becomes clearer, as will be discussed below.

Parenthetically, another factor that contributed to the misleading impression that all antidepressants are the same was the development of the Hamilton Rating Scale for Depression (HAM-D). This scale began to be used widely in clinical trials only at the end of the 1960s. If mild-to-moderate cases of depression are investigated using the HAM-D, then all antidepressants can appear the same, in the sense that they all lower the HAM-D total score by approximately the same amount. When more severe cases of depression are studied, this equivalence breaks down. The equivalence also fragments when large databases are assembled and correlation of clinical features with antidepressant selectivity becomes possible. When such correlation is done, features such as anergia and anhedonia can be shown to predict response to agents active on the catechol-

amine system. The homogeneous picture also collapses when affective disorders are studied against a full background of personality variations. Here it becomes clear that type of temperament predicts up to 50% of the variance in responsiveness to an antidepressant (Table 1).

The SSRIs pose a further problem for amine lesion models. On the basis of such a model, it is difficult to account for the efficacy of the SSRIs in obsessive-compulsive disorder, posttraumatic stress disorder, body dysmorphic disorder, social phobia, panic disorder, and anxiety and mood disorders. The SSRIs clearly work for these other disorders and do so in the absence of a significant depressive element. In some of these disorders, the treatment effect size of some SSRIs appears to be greater than it is in depression. If it is necessary to postulate action on some lesion to account for the usefulness of SSRIs for these various conditions, then lesions would have to be multiplied around the brain in plausible sites.

An alternative approach is that SSRIs have only a single action and that this is useful across a range of clinical disorders. I have referred to this action of the SSRIs as
 Evidence has been available since the late 1980s as to what the physiologic underpinnings of this therapeutic effect might be. Chouvet and colleagues, for example, were able to show in an elegant series of experiments that serotonin dampens down locus ceruleus responsiveness to glutamate, the natural excitatory neurotransmitter for the locus ceruleus.

This type of action can explain the efficacy of an SSRI in PTSD, in which a range of environmental triggers stimulate these kind of responses in the locus ceruleus. Reducing the response to glutamate is also useful for the depressed patient who has an obsessional streak. In such cases, it can be useful to reduce reactivity to the hundreds of triggers in the environment that have previously stimulated obsessional worries and ritualizing. Obsessional individuals would very likely experience this effect as wonderful—as leaving them feeling “better than well.” Indeed, it may in fact enhance their social functioning.

This effect would, however, be much less desirable in a more extroverted kind of personality, in which decreased responsiveness to the environment is more likely to be interpreted as emotional blunting. In this case, such an action would contribute to a reduction in the sense of well-being. Individuals affected in this way might show some improvement in that the core features of their illness may improve. However, on closer questioning, while reporting that there has been some improvement, they will be clearly aware that they have not been restored to normal. In clinical practice, it is not uncommon to have patients receiving an SSRI who, while remaining markedly depressed, comment on the unusual finding that for some reason they no longer seem to cry as much. Similar reports may come from recovered patients who are pleased to be well but, nevertheless, complain about an inability, for instance, to cry when appropriate. Changing treatment for such patients to a drug with minimal or no actions on the serotonergic system will often lead to spontaneous reports of a recovery of feelings. While emotional blunting does not feature on current lists of side effects, it may occur in up to 25% of patients. This estimate is derived from the speculation that the changes in sexual functioning brought about by SSRIs, which occur in up to 50% of those on SSRI treatment, can plausibly be attributed to the same mechanism.

There are good physiologic grounds to posit just such differential responses to selective antidepressants based on personality type. Twenty years ago, books on psychiatry were full of pictures of endomorphs, mesomorphs, and ectomorphs. It was thought that the constitutional type of the patients predicted what illnesses they would get. These ideas have not been supported, but the inverse idea—that constitutional type might predict response to treatments—is receiving increasing support. In the near future, psychiatric textbooks will be filled with graphs like those recently produced by Farde and colleagues showing that in a group of healthy volunteers, there is a range in dopamine-2 (D2) receptor numbers and that this range correlates with aspects of personality (Figure 3). This finding has already been confirmed. If the correlation is true for D2 receptors, it may also hold true for the various serotonin and catecholamine receptors. If monoamine receptor densities correlate with aspects of personality, it follows that they are also likely to correlate with what kinds of people respond to which type of antidepressants. Evidence obtained in clinical trials has already begun to show that this is indeed the case.

ANTIDEPRESSANTS AND WELL-BEING

Although reserpine has good credentials as an antidepressant, it clearly did not produce a sense of well-being in all who took it. Of note, however, is the fact that at the same time as Delgado and colleagues began to carry out tryptophan depletion studies and to use α-methylparatyrosine (AMPT) to produce “depressions,” some of the same researchers also administered reserpine to depressed patients. The reserpine investigation was carried out because there had been a number of reports across the United States that reserpine was of significant benefit in resistant depressions. These researchers ran a study of reserpine augmentation in patients who had failed to respond to standard treatments. The study did not show that the addition of reserpine was statistically significantly superior to placebo, although there was a trend in this direction. This trend and widespread clinical use strongly suggest that lowering serotonin and/or catecholamine levels in people who are depressed can be a good thing, i.e., can alleviate depression. So why should monoamine lowering cause a problem in some instances and not in others?

A study conducted in North Wales offers some pointers. We randomly assigned a group of 60 healthy volunteers to

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Figure 3. Correlation of Dopamine-2 (D2) Receptor Density and Detachment

Reprinted from Farde et al., with permission. “Detachment” values from the Karolinska scale of detachment (one of 15 Karolinska Scales of Personality) after adjustment for effects of gender.
receive a single dose of droperidol, 5 mg, lorazepam, 1 mg, or placebo. All those who received droperidol became akathisic and more than half of them became dysphoric. Five subjects became clearly depressed. They not only experienced dysphoria, anxiety, and an inability to sleep, but they clearly recruited depressive cognitions. Four subjects became suicidal within 2 or 3 hours of taking the drug. Three subjects remained affected by droperidol 1 week later, and 1 subject experienced effects for 3 weeks after receiving droperidol. Distinguished psychopharmacologist Merton Sandler, commenting on his experiences in the days when it was more common for psychopharmacologists and psychiatrists to try these drugs themselves, reported that after a single dose of reserpine he had become paranoid and aggressive for 4 weeks (M. Sandler, F.R.C.P., F.R.C.Psych., written communication, 1998).

Both droperidol and reserpine can be useful in the treatment of depression, but both also can cause significant dysphoria. A possible interpretation of the Yale depletion studies is that they triggered dysphoric responses rather than actually making people clinically depressed. In fact, from the early reports of the problems caused by reserpine, it is much clearer to the modern eye that reserpine did not make people depressed, but rather made subjects akathisic, with increased restlessness, insomnia, and a feeling of great discomfort. Observers simply did not know how to categorize these reactions during the 1950s or even the 1960s. Against this background, it was very easy to believe reports that reserpine made people depressed.

Is it important that reserpine made people akathisic rather than depressed? The contention of this article is that it is extremely important. The observations concerning reserpine illustrate that what might be the right antidepressant for one person may be the wrong one for another. This issue may be of distinct importance in efforts to reduce suicides associated with antidepressant treatment (Table 2).

Isacsson and colleagues reported on all possible suicides that occurred in Sweden in 1990–1991. There were 3400 cases of suicide in total, and approximately half (1700) would be expected to have a mood disorder. However, only 542 of these were found postmortem to have been receiving an antidepressant. Clearly, a considerable amount of work must still be done to make sure that people who are depressed get treatment. However, it is clear that a huge variation also exists in the frequency with which these antidepressants were associated with suicide. Lofepramine, which is more selective for noradrenergic reuptake inhibition, was associated with suicide much less frequently than other agents in this study.

Isacsson’s figure for individuals committing suicide on lofepramine treatment (41/100,000 patient-years) was replicated almost exactly in the United Kingdom (47/100,000 patient-years) by Jick et al. In that study, death by suicide after 172,000 prescriptions for antidepressants in primary care in the United Kingdom was investigated. The number of cases of suicide in conjunction with treatment with other drugs, including fluoxetine, mianserin, trazodone, and fluoxetine, was considerably higher. At that time, these were the drugs that primary care physicians in the United Kingdom could have been expected to give to people who they thought were at risk of suicide because of their safety in overdose. When factors associated with suicide, such as age, sex, and previous efforts to commit suicide, were taken into consideration, the number of patients per 100,000 patient-years fell for mianserin, trazodone, and fluoxetine as expected. The figure for fluoxetine, however, remained unchanged. Thus, although fluoxetine may be an extremely effective antidepressant for some patients and may restore some people to a state that is “better than well,” it is clearly not the right drug for all depressed people. National campaigns to detect depression and to treat it need to be supplemented by campaigns to ensure that the effects of therapy are monitored, especially during the early weeks of treatment. We have more work to do in terms of trying to make sure that patients receive the right drug for them, rather than simply expecting that any drug will do.

This view of antidepressant effects is consistent with a view first put forward by Angst and colleagues. Their view was not that antidepressants correct a lesion in people who are depressed, but that they create conditions in which people who are depressed can get well. The SSRIs, by reducing emotional reactivity, create one set of conditions that can be appropriate for many people who are depressed, but may not be helpful for all people who are depressed. Drugs active on the catecholamine system create a different set of conditions. The catecholamine system has been referred to as “the engine of the brain,” the system that produces “get-up-and-go.” Drugs active on this system are more likely to produce “get-up-and-go” than drugs active on the serotonin system. These drugs will not be the right treatment for all people who are depressed, but, as the studies comparing reboxetine and fluoxetine using the Social Adaptation Self-evaluation Scale demonstrate, clinical trials indicate that a higher proportion of

![Table 2. Antidepressant Outcomes: Suicide and Associated Risk](https://www.jclinpsych.org/content/61/10/1.supp)
patients receiving reboxetine get better and experience well-being than do those receiving fluoxetine.42

If the view held by Angst and colleagues is correct, it must be borne in mind that antidepressant drugs not only create the conditions in which people who are depressed get well, but they also continue to create the conditions after the subject has recovered. In fact, the depressed patients will spend more time on treatment during the maintenance phase, when they are symptom-free, than during the acute symptomatic phase. Therefore, the quality of the effects that their treatment produces during the continuation and maintenance stages of treatment is of supreme importance for compliance with treatment, reducing relapse risk, and, in general, influencing the quality of life of that individual over what may be a lengthy period of time receiving treatment.

Drug names: amitriptyline (Elavil, Lentizol, and others), chlorpromazine (Thorazine, Largactil, and others), clomipramine (Anafranil and others), desipramine (Norpramin, Perto-ram, and others), fluoxetine (Prozac, Fluclint), isoniazid (Rifamate and others), lorazepam (Ativan and others), nortriptyline (Pamelor, Allegron, and others), protriptyline (Vivactil, Concordil), reboxetine (Vestra, Eronax, and others), reserpine (Serpalis and others), trazodone (Desyrel, Molipaxin, and others), trimipramine (Surmontil).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, the following agents are not approved by the U.S. Food and Drug Administration for the treatment of depression: chlorpromazine (Serpasil and others), trazodone (Desyrel, Molipaxin, and others), nortriptyline (Pamelor, Allegron, and others), protriptyline (Prozac, Fluctin), isoniazid (Rifamate and others), lorazepam (Ativan and others), desipramine (Norpramin, Pertrofan, and others), fluoxetine (Seroxat, Prozac, Fluclint), and others, which may be termed experimental drugs.

REFERENCES
14. Klein DF, Fink M. Psychiatric reaction patterns to imipramine. Am J Psychi-