How Fast Are Antidepressants?

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Background: For years, investigators have tried to determine the speed of onset of antidepressant drugs. Claims that particular drugs may produce a faster response in patients than other agents have been made, but such claims have never been confirmed.

Method: The authors reviewed reports from studies of the speed of onset of antidepressant therapies and other studies that revealed information on this topic. We compiled a list of factors that can affect the results of such studies and interpretations of study results. In addition, we reviewed literature concerned with methods of speeding up antidepressant responses.

Results: No antidepressant medication currently available has been shown conclusively to have a more rapid onset of action than any other. However, some methods of augmentation may have the potential to speed responses. Somatic therapies such as electroconvulsive therapy, phototherapy, and therapeutic sleep deprivation may be the fastest options available at this time.

Conclusion: All available antidepressant medications are usually taken for several weeks before future responders will display a significant therapeutic benefit. If a patient does not show at least a 20% improvement within the first 2 to 4 weeks of treatment, the treatment regimen should be altered. For patients who do show early benefits from a medication trial, one can expect additional benefits to accrue over an 8- to 12-week period and to improve overall outcome compared with those slower to respond. Future trials need to address methodological confounds, but a truly "faster antidepressant" will probably require new neuroscience technology.

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As long as there have been antidepressants, there have been people who have claimed that one agent has a faster onset of action than another. Of the first-generation tricyclic antidepressants (TCAs), desipramine was initially reported to work most rapidly. In the early second generation, amoxapine received similar acclaim. In hindsight, neither claim withstood the test of time or rigorous science. Conceivably, the rapid onset of sedative or stimulant properties with a given drug may have contributed to such impressions during the period following the drug's release. In any case, arguing that the onset of one antidepressant's action is faster than another is only relevant if one sees a difference in measured endpoint when the compounds being compared are of equal efficacy and are dosed equivalently in clinically similar subjects.

In the 1980s, Quitkin and colleagues[1,2] analyzed the weekly global response pattern of patients participating in placebo-controlled antidepressant trials. The pattern of response that distinguished drug responders from placebo responders was a several-week delay in onset and a nonfluctuating course. This "pattern analysis" suggests that a true antidepressant drug response (as opposed to a placebo response in a patient taking an antidepressant drug) has a several-week lag from treatment onset.

Quitkin's requirement of "much improvement" on the Clinical Global Impressions scale (CGI) as an indicator of improvement is relatively strict. Contrary findings were reported by Stassen and coauthors[3] in 1993, who used a "survival analytical approach" to conclude that there is no delay in onset of activity of antidepressants. Unlike Quitkin's group, Stassen et al.[3] required only a 20% reduction in the Hamilton Rating Scale for Depression (HAM-D) score as an indication of onset of activity, or time to improvement, which may have biased their findings since it is possible that early sedative or stimulant effects of the antidepressants could account for observed reductions in HAM-D scores. Likewise, the lag observed by Quitkin et al.[1,2] may be artifactual, caused by the high degree of improvement required to define a response in their study. In other words, the Stassen group's use of a different endpoint than Quitkin's group may help to explain the divergence in conclusions drawn from their respective studies.

The analyses by Quitkin et al.[1,2] have been further criticized by Katz and coworkers,[4,5] who drew on data from the National Institute of Mental Health (NIMH) collaborative study of the psychobiology of depression, as well as other work. Rather than confirming a "lag time" until true

drug effect is achieved, these investigators found evidence of improvement after 2 weeks (and in some symptoms after just 1 week), which suggests a pattern of gradual alleviation and step-by-step eradication of symptoms until full remission is ideally achieved after additional weeks of treatment.

Some of the earlier claims made about one antidepressant's having a faster onset of action than another came from studies that were actually designed to measure efficacy and safety, not onset of action, and were based on measurements taken only once a week. However, even studies specifically designed to measure time to onset of antidepressant action have also measured many other variables, and, therefore, no general conclusions can be drawn from the often conflicting findings.

We, therefore, reviewed reports from studies of the speed of onset of antidepressant therapies and other studies that revealed information on this topic. From these studies, we compiled a list of factors that can affect the results of such studies and interpretations of study results. In addition, we reviewed literature concerned with methods of speeding up antidepressant responses.

SPEED OF ONSET OF ANTIDEPRESSANTS: FACTORS AFFECTING RESULTS OF STUDIES

Definition of Efficacy

Before the onset of efficacy can be measured in a given study, a definition of efficacy must be established. Differences in efficacy criteria between studies make it difficult to compare findings. In addition, if only the first response is recorded and further improvements are not measured, true responses cannot be reliably differentiated from placebo responses or random fluctuations of symptoms. How efficacy is defined and measured depends greatly on the rating scale used in the study, as different scales tend to weight symptoms differently. For example, the HAM-D has a heavy emphasis on somatic symptoms compared with the Montgomery-Asberg Depression Rating Scale (MADRS).

Montgomery[6] suggests several possible methods for defining onset of improvement in a theoretical study. One definition is a 25% reduction in initial severity scale score, since this is half of the 50% improvement criterion widely used to define responders in acute treatment studies. An alternative definition is a 4-point reduction in MADRS or HAM-D scores. The latter suggestion is problematic in that a severely depressed person will be less likely to have a clinically significant improvement with a given number of point reduction, while a mildly depressed person with the same point reduction might fall into the partial-responder category.

Rating Scale Used

Some scales, such as the MADRS, are more sensitive to change in mood than others and, therefore, might shorten observed improvement delays more than that seen in a study using a less sensitive scale. Some items on depression rating scales may be preferentially influenced by medication side effects, indicating an improvement in depression before a real response has occurred. For example, the HAM-D contains many sleep-related items that could be affected immediately by a sedating antidepressant. In this situation, patients might show a significant change on the total HAM-D score owing to improved sleep, but have little or no improvement in mood.[2] Also, evidence suggests that patients may detect improvements in their own conditions sooner or later than physicians or family members, so patient self-rated scales might tend to show a different rate of onset of improvement than observer-rated scales. When using observer-rated scales, interrater reliability may also be a problem, especially if a study is conducted by multiple centers.[7]

Along with other investigators who have criticized aspects of some rating scales for studying depression response to treatment, Healy and McMonagle[8] suggest that one of the reasons it has been difficult to demonstrate differential speed of onset of antidepressants is that the scales normally used do not measure some domains of functioning which may be affected early in treatment, such as interpersonal functioning. They argue for using more patient-reported measures, specifically the Social Adaptation Self-Evaluation Scale, to more adequately capture efficacy in the social domain.

Frequency of Measurement

In most studies of antidepressant efficacy, the time interval between successive observations or clinical measurements is usually 1 week. This may not be frequent enough to capture a possible difference in the speed of onset of activity in different antidepressants.

Method of Analysis

In analyzing data from any study of the speed of onset of antidepressant response, the type of data analysis will influence the results. Among other factors, time may be treated as either an independent or a dependent variable.

Time series analysis. This methodology allows each individual subject's course of improvement to be modeled in detail and can help to solve statistical problems, such as the serial dependency on time series data. However, it is sometimes difficult to meet the requirements that must be fulfilled before this kind of analysis can be performed, such as the need for a high number of evenly spaced successive observations.

Survival analysis. This type of analysis involves the use of a collection of statistical techniques applied to positive random variables that represent the time to an event of interest (i.e., onset of antidepressant action). In survival analysis, the probability distribution of time to the occurrence of the event is modeled, and the probabil-

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ity that the event occurs at a given time or later time is called the *survival distribution*. This includes dropout cases and the effect of time to withdrawal from the study. According to Overall,[9] the survival analysis model works best when examining average times to some discrete endpoint (such as death). Since the effects of antidepressant drugs are usually measured on a graded continuum, applying survival analysis techniques to these measures of clinical response forces investigators to translate these data measured across time into a more discrete, dichotomized data set (i.e., defining the onset of antidepressant action as theendpoint of interest). The dichotomized data would represent times at which the patient would fall in the responder category and times at which the patient would not. This approach does not take full advantage, therefore, of information gathered from repeated measurements across time. Likewise, if one were investigating the persistence of response to antidepressant therapy (which would also involve multiple measurements on a continuum over time), using survival analysis to look at this issue might also be of limited usefulness.[9]

Pattern analysis. This type of analysis takes into account individual courses of improvement and differentiates between placebo and drug effects. It allows for the identification of patients who have early persistent responses, delayed persistent responses, or no responses to drug therapy.

Regression model. In the analysis of variance (ANOVA) regression model, assessment times are represented as fixed independent variables, a test of statistical significance for differences in rates of symptom reduction is provided, and estimates of the period of time corresponding with any specified level of improvement are based on regression lines fitted to all of the available quantitative data for each subject. This model allows for more complete use of the data collected over time, rather than reducing the data to a single dichotomized score as in the survival analysis technique.[9]

As an illustration of the different results that can be obtained using different models of data analysis, Nobler et al.[10] used 4 different models to look at response to electroconvulsive therapy (ECT). Depressed patients (N = 96) were randomly assigned to receive right unilateral or bilateral ECT with stimulus intensity just above (low-dose) or 150% above (high-dose) initial seizure threshold.[10] (Low-dose right unilateral treatment was not included in the analyses owing to inadequate response to this treatment.) ECT was continued until a patient was asymptomatic or showed no further improvement over at least 2 consecutive treatments. A patient who showed no response after 10 treatments was labeled a nonresponder. The number of treatments administered ranged from 3 to 17.

The methods of data analysis used were (1) ANOVA on slopes of linear regression of HAM-D scores against treatment numbers, (2) random regression modeling, (3) ANOVA on time to achieve cutoffs of clinical improvement, and (4) survival analysis. When the data were analyzed using ANOVA on slopes, no statistically significant difference was found in the rate of symptomatic change between the 3 groups of patients. Factors that may have contributed to the apparent insensitivity of this particular analysis include the fact that the plotted pattern of symptom change over time was nonlinear in many patients (there were transient fluctuations in HAM-D scores for individuals) and that the data were organized using the measured rate of change in HAM-D score rather than the percentage of improvement in symptoms.[10]

When random regression modeling was used to analyze the data and only patients receiving more than 8 treatments were included, there appeared to be no statistically significant differences between the experimental groups. For patients receiving 8 treatments, a trend emerged in which those who received high-dose bilateral ECT were represented by a regression line with a steeper slope than those treated with low-dose bilateral ECT. For patients receiving 6 treatments, the difference was statistically significant, suggesting faster improvement with high-dose bilateral than with low-dose bilateral ECT early in the course of treatment.[10]

The "ANOVA on time to cutoffs" analysis looked at the number of treatments administered prior to reaching and maintaining 30%, 40%, 50%, 60%, and 70% decreases in HAM-D score from baseline. For time to a 30% reduction in HAM-D score, there appeared to be no major differences between treatment groups. For time to 40% reduction, high-dose right unilateral ECT required fewer treatments than low-dose bilateral ECT. The difference in time to reach cutoff became significant for time to 50% reduction: high-dose right unilateral and high-dose bilateral treatments were "faster" (required fewer treatments) than low-dose bilateral ECT. There was no longer any main difference between treatment groups for time to 60% or 70% reduction in HAM-D scores.[10]

In the survival analysis, events were defined as sustained 30%, 40%, 50%, 60%, and 70% decreases in HAM-D score from baseline. Patients not reaching these levels were treated as censored at the time of last treatment. This yielded an effect of ECT treatment modality for time to reach the 30%, 40%, 60%, and 70% reductions in HAM-D scores. In each, time to event was significantly shorter for patients treated with high-dose bilateral ECT than for those receiving low-dose bilateral ECT, except for the 50% reduction group, which failed to reach statistical significance (probably representing a type 2 error).[10]

The "take-home message" of the Nobler et al.[10] study is that the statistical method chosen to analyze the speed of improvement in HAM-D scores can strongly influence whether or not differences between treatment modalities are observed at all and whether or not these differences are determined to be statistically significant.

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Anyone studying the speed of onset of antidepressants must deal with the problem of patients who never achieve adequate benefit from their treatment. According to Laska and Siegel,[11] findings must be divided into the proportion of patients who will not reach onset of clinical improvement and the distribution of time to onset for those who will. The median time to improvement onset will be shorter in a group of patients who will all eventually reach onset than in a group in which some patients will never reach it. Survival analysis can be used to determine that a patient will likely never obtain a significant therapeutic benefit from an antidepressant if the onset of action has not occurred within a given period of time.

Sometimes, using alternative models of data analysis will lead to consistent interpretations. In one example, a meta-analytic study of depressed patients, Stassen et al.[12] compared fluoxetine and moclobemide head to head using 2 competitive statistical methods: mixed linear regression and survival analysis. Both analyses provided evidence that the 2 treatments were equal in terms of efficacy, number and timing of study dropouts, and time to improvement and recovery. They noted that the equivalent results were similar to those they had found in looking at the meta-analytic data for imipramine, amitriptyline, oxaprotiline, and placebo. They also noted that the results of the study suggest that early improvement may be predictive of future response in individual subjects.[12]

Comparator Drug

If one antidepressant is compared with another in terms of speed of action, the findings can only show which, if either, of the 2 drugs is faster, not that one drug is faster than other antidepressants or even faster than placebo. It is also important that the agents compared are used at doses and with titration schedules that are comparable. Comparison of 2 (or more) active treatments and placebo allows for more generalizability.

Dose and Dosing Strategy

The amount of time that passes before subjects reach a therapeutic dose of medication during a study will affect when a response will likely occur and in how many subjects a response will be obtained. Titrating too slowly may lower the rate of early response, whereas titrating too rapidly might increase the dropout rate before a response can be produced or noted secondary to side effects.

In a study by Benkert and colleagues,[13] 167 inpatients with major depression and melancholia were treated with rapidly escalating doses of venlafaxine or imipramine in a double-blind, randomized, parallel study. Venlafaxine was increased to 375 mg/day over 5 days, maintained for 10 days, and then reduced to 150 mg/day for the rest of the study period. Imipramine was increased to 200 mg/day over 5 days, then maintained throughout the study. Clinical response was defined as a decrease of at least 50% on the HAM-D or MADRS. Patients who were considered to be responders on the basis of HAM-D scores had a median time to response of 14 days for venlafaxine compared with 21 days for imipramine. However, no statistically significant difference was noted between the 2 groups in median time to response based on MADRS scores, leaving the overall results ambiguous.

Entsuah and others[14] report on 2 double-blind, placebo-controlled studies that also used high daily doses of venlafaxine. In both studies, venlafaxine was titrated to 200 mg/day within the first week. Drug response was defined as a score of 1 (very much improved) or 2 (much improved) on the 7-point Global Improvement item of the CGI. Employing pattern analysis to examine sustained responses to treatment, the authors found that significantly greater percentages of venlafaxine-treated patients compared with placebo-treated patients had a clinically meaningful drug response within the first 2 weeks of treatment: 27% versus 9% in Study 1 and 20% versus 2% in Study 2. The absence of a comparator drug, however, leaves open the question of whether venlafaxine works faster than other antidepressants.

Katz and coauthors[5] noted that in the analyses by Quitkin et al.,[1,2] which perceived a "lag time" in the "true" antidepressant response, maximum doses of TCAs were not achieved until after 15 days of treatment in a majority of patients. In the NIMH collaborative study,[5] by contrast, 80% of patients received even higher TCA doses by the end of the first week. However, this difference most likely reflects the fact that faster titration of medications can be accomplished in an inpatient setting (Katz et al.[5]) than an outpatient setting (Quitkin et al.[1,2]).

Significant differences in dosing strategy between groups or individuals, even using a single agent, can bring about different speeds of onset of antidepressant response. A provocative exploratory study inspired by the observation of rapid improvement of depressive symptoms after 2 patients survived TCA overdose illustrates this point. Malhotra and Santosh[15] showed that oral pulse-loading of imipramine brought about a more rapid response than the usual slow imipramine titration, using HAM-D scores. While side effects were noted earlier in the pulsed group, tolerability was reported to be similar, and no significant toxicity was resultant from pulse-loading. The main limitations of the study are its small sample size (N = 16) and the lack of a placebo arm. However, it demonstrates that dosing strategy does make a difference and suggests that a closer look at the way in which we dose medications may help us to speed responses.[15]

Patient Characteristics

Patient characteristics may have a significant impact on the rate at which patients respond to treatment. Variables include the presence of chronic versus acute depression, severity and subtype (e.g., melancholic, psychotic)

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of depression, psychiatric or medical comorbidity, treatment with additional medications, and prior exposure to the particular drug being studied.

An example of a study in which patient characteristics prove especially salient is a double-blind study by Keller et al.,[16] in which 635 outpatients with chronic major depression or double depression were randomly assigned to 12 weeks of treatment with either sertraline or imipramine. Approximately 21% of the patients who had achieved a therapeutic response at week 12 had not done so at week 8, suggesting that patients with chronic depression may take longer than those with acute depression to respond to medication. It is important to note that most of these patients had *begun* their improvement earlier (vide infra). Patients with an unsatisfactory response to the initial medication after 12 weeks of treatment were crossed over to the alternative medication for another 12-week trial.[17] Patients who responded during either the initial acute phase trial or the crossover trial were entered into a 4-month continuation treatment study arm. Sixty-seven percent to 70% of patients who entered the continuation arm in full remission remained stable, and over 40% of those who entered in partial remission reached full remission, suggesting continuing accrual of antidepressant benefit in this population during months 4 through 7 of treatment.[18] However, the group of patients who were crossed over from the initial drug to the alternative one prior to the continuation phase were less likely to have kept the benefits accrued or continued to improve, as were patients in the group who responded to the initial drug. The study findings suggest that patients with chronic depression will be more likely to have a slower response to treatment than more acutely ill patients.

Sample Size

If the onset of significant mean activity in a subject sample is being measured rather than the mean and distribution of the onset of activity, then the sample size becomes very important. The time at which treatment effect first achieves statistical significance will occur earlier in a sample of 500 than in a sample of 50. Studies with large samples, therefore, will have greater power to detect small differences in speed of onset between antidepressants.[19]

Duration of Study

Montgomery[6] has proposed that 2-week trials would be sufficient to measure efficacy if measurements were obtained twice weekly and the optimum response group were studied. (The optimum response group would be defined as having a low placebo response rate, severe depression, and stable depression severity on entry.) One advantage of a 2-week trial as opposed to longer ones is a decrease in the length of exposure to placebo, which would resolve some ethical concerns about treating severe illness with placebo when other agents have been proved more effective. Two-week trials would need to be followed by longer-term studies to establish the degree to which response is sustained.

Early response to an antidepressant appears to predict whether or not a patient will achieve remission. This principle can be used to determine whether therapy should be altered (e.g., dose adjusted, antidepressant switched) after several weeks. Stassen and coauthors[20] found that 70% of subjects who showed improvement of at least 20% at 10 days reached the conventional 50% symptom reduction/responder criterion at 4 weeks. A recent study by Quitkin et al.[21] investigated at what point a patient will likely receive no further benefit from a given antidepressant and should be switched to another. Quitkin's group[21] studied a total of 593 patients to determine the time at which patients who received drug therapy would have a better chance of being rated as responders versus patients who received placebo. Data were obtained from studies conducted at an outpatient research clinic affiliated with Columbia University at the New York State Psychiatric Institute over a 10-year period. All included studies were double-blind, lasted for 6 weeks, and used a fixed flexible dose schedule. Medications included monoamine oxidase inhibitors, TCAs, and mianserin. Patients were rated using the CGI scale. One notable limitation of this study was that not all subjects received the maximum drug dose by week 3.

Nineteen (32%) of 59 drug-treated patients who were unimproved at week 3 were rated as responders at week 6 versus only 6 (10%) of the 57 placebo-treated patients. Interestingly, the effects of drug therapy and placebo appeared to be equal for patients who showed no improvement by week 4. However, drug-treated patients who did not respond by week 4 but had been minimally improved at some earlier point still had a superior prognosis over placebo-treated patients through week 4; 39% of drug-treated patients in this category versus 8% of placebo-treated patients were rated as responders by week 6. These observations were consistent across diagnoses and drug class. On the basis of their findings, Quitkin and coauthors[21] recommend that patients who are tolerant of an adequate dose but whose conditions have not been even minimally improved by the end of week 4 should have their treatment regimen altered. Patients who show minimal improvement early but not after week 5 should also have their treatment regimen changed.

The results of an open trial of fluoxetine (20 mg/day) by Nierenberg and others[22] support these recommendations. They found that of the patients who showed no improvement at weeks 2, 4, and 6, the proportions of responders at week 8 were 36.4%, 18.9%, and 6.5%, respectively. Response was defined as the usual 50% or greater decrease in score from baseline on the HAM-D. These investigators suggest that for patients who show no improvement after 4 to 6 weeks of taking a standard dose

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of fluoxetine, extending the trial under the same conditions is not justified. Instead, they recommend increasing the dose of fluoxetine, augmenting the trial with other agents, or switching to another antidepressant altogether.

In a double-blind, parallel-group study comparing fluoxetine with desipramine in patients with major depression, Bowden and colleagues[23] assessed whether improvement relatively early in treatment was predictive of categorical response at 6 weeks. For fluoxetine-treated patients (but not for desipramine-treated patients), change in item 1 (depressed mood) of the HAM-D at week 3 was significantly predictive of response (again, at least a 50% reduction in HAM-D score from baseline) at week 6.

Katz and others[4] found that reductions in anxiety and hostility after 1 week of antidepressant treatment predicted response at 4 weeks of treatment. They suggest that the absence of significant improvement after 2 weeks of antidepressant treatment makes a response unlikely after a more prolonged period and dictates the need for a change in clinical strategy.

META-ANALYSES

It is worth noting that meta-analyses are fraught with problems in the categories we have discussed. For example, a meta-analysis[24] of 20 short-term (2- to 26-week) studies of selective serotonin reuptake inhibitor (SSRI) efficacy reports that 5 of the studies support the likelihood that fluoxetine onset is slower than that of its cousins. Theoretically, given fluoxetine's long half-life and the fact that it therefore takes longer than the other SSRIs to reach steady state, this report may have a valid basis. However, the meta-analytic nature of the study makes this claim preliminary, at best. The studies compared are of different durations, use different rating scales, are not all placebo-controlled, and differ widely in sample sizes and statistical analytic methods. Since meta-analyses attempt to compare large amounts of data in order to draw clinically relevant conclusions, they can be valuable for determining possible future investigative questions. That article suggests it would be worthwhile to design prospective placebo-controlled studies to look at variable speed of SSRI onset to determine whether in fact fluoxetine is slower than the other SSRIs.

RECENT CLAIMS: MIRTAZAPINE

In a review article about mirtazapine's role in depression treatment, Holm and Markham[25] comment on mirtazapine's unique mechanism of action paired with the observation from animal studies that after its administration, increased rate of firing of serotonergic neurons is observed (compared with the opposite observation after SSRI administration). They go on to discuss preliminary (including some unpublished) data that showed more rapid improvement in weeks 1 and 2 for mirtazapine over paroxetine and citalopram and faster improvement in weeks 3 and 4 in comparisons with fluoxetine.[25,26] The studies cited used the HAM-D and found that the mirtazapine group showed improvements over the fluoxetine and paroxetine groups on measures of anxiety/somatization and sleep. While it is tempting to conclude that mirtazapine may have a faster onset of action than the SSRIs for depression, it is most likely that mirtazapine's histaminergic side effect profile is responsible for these results. The same mechanism is likely responsible for the common adverse effects of mirtazapine, including increased appetite and weight gain, that are not seen to the same extent with the SSRIs.

Another study of mirtazapine,[27] building again on the observation of its association with increased serotonergic neuronal firing rate (which is thought to be the same mechanism by which pindolol may act to augment SSRI efficacy), used the MADRS as well as several other clinical rating scales to look at its efficacy compared with citalopram. The 8-week, double-blind, randomized study of patients with major depression in northern Europe used comparable doses of the 2 agents, finding equal efficacy at endpoint. The 2-week point was marked by statistically significant superiority of mirtazapine on the MADRS, the CGI, and the Hamilton Rating Scale for Anxiety, suggesting it may be faster acting than citalopram.[27] Unfortunately, the study did not include a placebo arm, so it is impossible to say that the early difference was not due to placebo effect, although the reasons this effect might be seen in one study arm and not the other are unclear. Because there were differences between the 2 groups in terms of gender and incidence of recurrent depression, the comparison becomes even more problematic.

Despite many preliminary suggestions that mirtazapine may be faster acting than other antidepressant agents according to multiple studies designed to look at efficacy,[28,29] we are unaware of any study to date that has been designed specifically to investigate this claim prospectively. If a study were designed to attempt to look at speed of onset of antidepressant agents in comparison to mirtazapine, the study should attend to the factors discussed above, using a double-blind, randomized design with comparable sample sizes, patient characteristics, and dosing regimens and should include a placebo arm. The optimal study would use frequent observations on multiple scales (both patient report and observer rated) with special attention paid to symptom clusters in depression and would show equal efficacy of mirtazapine and comparison agents at endpoint over placebo.

AUGMENTATION STRATEGIES AND SPEED OF ONSET

Pharmacologic Augmentation

Many investigators have looked for pharmacologic augmentation strategies that hasten antidepressant re-

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sponse. One of the factors that makes the literature difficult to interpret in terms of the speed-of-onset issue is that most studies on augmentation have been performed in patients who are treatment resistant. These studies use augmenting agents as additions to regimens when subjects fail to respond within a certain amount of time, so they do not effectively address the time to initial onset. Only when antidepressant medication is used in addition to an augmentation agent versus placebo at study initiation can a study reliably say something about onset of action with augmentation. Ideally, these studies would also need to attend to all the same issues we have already discussed for head-to-head prospective studies.

In a review article examining polypharmacy and the question of whether or not combination treatments may hasten antidepressant responses over monotherapy options, Dufresne[30] summarizes many of the issues that are problematic in performing and interpreting studies of combination therapy. He points out that it can be exceedingly difficult to tease apart why or how drug combinations may be affecting a given patient. For example, when "augmenting" an SSRI with trazodone at the start of antidepressant therapy, it might be said that trazodone is being used to help specifically with depression-associated insomnia. However, the combination of pharmacologic actions may be working on depressive symptoms synergistically to improve the response to pharmacotherapy as well. He states that lithium and triiodothyronine (T_3) augmentation may be most helpful in speeding the onset of antidepressant response. In terms of lithium augmentation of SSRI or TCA treatment, he comments that most studies do not look at whether or not lithium alone may produce the same effect, which is sometimes observed to be a faster onset of action than is seen with nonlithium monotherapy. He calls for the performance of specific prospective trials comparing the combined use of norepinephrine reuptake inhibitors (NRIs) with SSRIs versus monotherapy in terms of investigating differential speed of onset of the 2 approaches.[30] This proposed study, as well as others that look at other augmentation approaches, will help to form evidence-based strategies for rational combination antidepressant therapies in the future.

Lasser and Baldessarini[31] reviewed the literature to address thyroid hormone usefulness in the treatment of depression. A handful of studies, which have inexplicably not been replicated or pursued, showed that early addition of T_3 or intramuscular injection of thyroid-stimulating hormone at the start of treatment with a TCA may speed onset of action compared with TCA treatment alone. Further studies are clearly needed to investigate the usefulness of thyroid axis agents in achieving timely response for depression, especially in specific subtypes of patients.[31]

It has been hypothesized that inositol augmentation of SSRI therapy may help to overcome treatment resistance and speed onset of action by modulating the intracellular phosphatidylinositol second-messenger system for 5-hydroxytryptamine-2 (5-HT_2) receptors. Levine et al.[32] performed a small study (N = 27) to examine this hypothesis. Their results showed no faster improvement with inositol than with SSRI treatment alone. Their review of the literature also indicated poor results in speeding the action of antidepressants with both pindolol and thyroxine (T_4), and they acknowledge only sleep deprivation as an augmentation strategy that "rapidly" alleviates depression.

In terms of pindolol augmentation of standard antidepressant therapy, several studies have looked at the speed of onset of antidepressant response. Perez et al.[33] tried to induce rapid response in SSRI-treatment-resistant patients using pindolol augmentation. No statistically significant difference was noted with pindolol versus placebo addition after 10 days.[33] However, since this study did not initiate pindolol versus placebo at the start of treatment, and because the patients were specifically noted to be treatment resistant, the study says little about whether pindolol augmentation might speed response in other situations.

In a study[34] of depressed patients with psychotic features, those who received both fluvoxamine and pindolol after placebo run-in had significantly better response as measured by HAM-D and the Delusional Experience Rating Scale at weeks 3 and 4 compared with those who were treated with fluvoxamine and placebo. Interestingly, the difference between the 2 groups cannot be explained by different blood levels of fluvoxamine, since levels were equivalent for both groups. It is also important to note that the 2 groups were equal in response rate at study completion (approximately 80%).[34] While the study was small (N = 71) and remains to be replicated, it suggests that augmentation of SSRI treatment with pindolol at initiation of treatment may speed responses in psychotic depression. Whether or not this result might also be seen in nonpsychotic depressed patients remains to be seen.

In another small study from France,[35] initiation of treatment in antidepressant-naive patients using paroxetine and pindolol augmentation showed greater improvement by day 10 than in those treated with paroxetine and placebo. By day 15, the difference between the 2 arms disappeared. The study successfully demonstrates many of the specifications for careful investigation of speed of onset, including using frequent measurements of symptoms (every 5 days initially) and several rating scales (HAM-D, MADRS, and CGI).[35] Hopefully, the results of this study will be replicated and will inspire others to carefully design studies that further investigate the speed of onset issue. One might argue that 5 days' difference is clinically insignificant and that the increased cost of combination therapy over monotherapy cannot be justified for such a short-term benefit. However, aside from the fact

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that depressed patients treated with the combination strategy suffered quantitatively less than their monotherapy-treated counterparts for 5 days, there may be other, less obvious benefits to speeding antidepressant effects. A 1-year prospective follow-up study of similar patients demonstrated that those with a faster initial response (the pindolol-plus-paroxetine group) also had a superior outcome 1 year later.[36] This outcome may be related to biological and psychological factors as well as differences in compliance. Theoretically, early responders might associate their early improvement with the initiation of medication more so than do those patients who responded later. This could set up better compliance in early responders and/or could extend the placebo effect into the long term in the early response group. Studies looking at these factors would be interesting and clinically helpful.

Augmentation With Other Somatic Techniques

The psychiatric literature is full of findings that support the rapid onset of antidepressant action of nonpharmacologic somatic therapies, including ECT, phototherapy, and therapeutic sleep deprivation. A small German study (N = 39)[37] of medication-resistant depressed patients showed a significantly quicker response to suprathreshold right-unilateral ECT, notable even in the first week of therapy, compared with patients treated with paroxetine. This was true for both phases of the study, the initial randomized phase and the open crossover phase.[37] One weakness of this particular study was its lack of placebo arms (placebo medication and sham ECT) in addition to some significant differences in quality of pretreatment (past medication trials) in the 2 groups of patients. Small sample size also weakens the power of the study, a factor that is often the case in studies involving somatic therapies, since such therapeutic interventions are often more labor and resource intensive than those in medication trials. Despite these concerns, the study supports other similar studies and clinical experience: ECT can be fast-acting for the treatment of depression compared with medications, even in treatment-resistant patients.

Some studies have looked at somatic techniques to augment pharmacologic therapies in terms of overall efficacy and speed of onset of benefits. Comparing pilot study data (e.g., nonrandomized, non–double-blinded) of elderly depressed patients who received sleep deprivation prior to antidepressant (paroxetine) treatment and similar studies of antidepressant monotherapy in elderly depressed patients, Green et al.[38] suggested that the combined treatment may lead to a response rate twice as rapid as that seen in the monotherapy groups. They call for more studies looking at the use of partial or total sleep deprivation to kickstart depression treatment.[38]

Perhaps the most promising treatments for depression in terms of speed of benefit onset is the use of combined partial sleep deprivation and bright light therapy, both nonpharmacologic interventions. Kripke[39] reviewed the literature on light treatment for nonseasonal depression and noted that while head-to-head prospective trials comparing medications and bright light are lacking, preliminary studies have shown dramatic benefits within 1 day to 1 week with the somatic therapies alone. He calls for more studies to show relative benefits of light therapy and alternatives, as well as longer-term placebo-controlled (using sham bright light therapy) studies of light treatment that would help establish that benefits are maintained. He also suggests that, despite the fact that supportive data are preliminary at best, combining light treatment with medication for unipolar depressives is clinically appropriate unless there is a specific reason not to do so.[39]

CONCLUSION

As it was in the 1950s, so it is at the turn of the century: all available antidepressant medications usually take several weeks to show a significant therapeutic benefit for most patients who will respond. Some benefit appears to occur within the first 2 to 4 weeks of treatment, and if a patient fails to show at least a 20% improvement by that time, treatment should be altered (e.g., increase the dose, augment with an adjunct, switch to another antidepressant). For patients who do show early benefits from a given treatment, additional benefit appears to accrue over at least 8 to 12 weeks. Chronically depressed and elderly patients may respond more slowly than patients with acute depression.[16,18,38] No antidepressant currently available has been proved to work faster than any other. Only somatic therapies such as ECT, phototherapy, and therapeutic sleep deprivation appear to work faster than antidepressant drugs. It is unfortunate that more research comparing these therapies is not currently underway, but perhaps this is not surprising given that much of the current research in depression is funded by the pharmaceutical industry.

Clearly there is a need for more focused research in terms of prospective studies looking at differential speed of onset of antidepressant treatments. Shortening the duration of acute depression is a worthy goal, since it speeds hope to individual patients and families, cuts down on costs of acute treatment in terms of hospitalization resources and lost time at work, and seems to predict better long-term outcomes with improved compliance and fewer relapses. It is likely that future investigations of specific agents will both further our efforts to understand the mechanisms behind agent activity on a molecular level and may provide clues how to better test agents for relative speed and efficacy.[40] Overall, studies designed to look at the speed-of-onset issue need to use clear definitions of actions, standardized methods, equivalent dosing of comparison agents, and adequate sample sizes to amass statistical power. In addition, it would be helpful to measure re-

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sponse to treatment with scales or methods that use more meaningful dimensions for depressive syndromes than some current measures, focusing specifically on symptom clusters rather than an overall score.[41]

Studies purporting to show that a new pharmacologic treatment works faster than other therapies will have to attend to the many methodological concerns outlined earlier. However, we can assume that a new treatment that produces a dramatically more rapid effect than existing therapies would be obvious even to the casual observer. Theoretically, new approaches to pharmacokinetic variables, such as drug delivery via skin patches, rather than oral ingestion or highly localized administration of medication, or electrical impulses into brain structures via psychosurgical techniques, might speed depressive symptoms away.[21] It is also likely that depression research of the near future will take advantage of other methods of assessing treatment response (rather than relying so heavily on clinical interviewing and rating scales), including functional neuroimaging techniques. The future of depression research will very likely include radically new approaches to adjust abnormalities in brain centers or neural networks that regulate mood. Shortening the time to benefit onset in depression treatment will continue to be a major goal for psychiatrists of today and tomorrow.

Drug names: amitriptyline (Elavil and others), amoxapine (Asendin and others), citalopram (Celexa), desipramine (Norpramin and others), fluoxetine (Prozac), fluvoxamine (Luvox), mirtazapine (Remeron), paroxetine (Paxil), sertraline (Zoloft), trazodone (Desyrel and others), venlafaxine (Effexor).

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