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Antidepressant Drugs and the Emergence of Suicidal Tendencies

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Summary

Although antidepressant medications represent the cornerstone of treatment for patients with moderate to severe clinical depression, they also carry serious risks. There is evidence which suggests that antidepressants can, in rare instances, induce or exacerbate suicidal tendencies. Nine clinical mechanisms have been proposed through which this may occur. These are: (a) energising depressed patients to act on pre-existing suicidal ideation; (b) paradoxically worsening depression; (c) inducing akathisia with associated self-destructive or aggressive impulses; (d) inducing panic attacks; (e) switching patients into manic or mixed states; (f) producing severe insomnia or interfering with sleep architecture; (g) inducing an organic obsessional state; (h) producing an or-

ganic personality disorder with borderline features; and (i) exacerbating or inducing electroencephalogram (EEG) or other neurological disturbances.

Epidemiological and controlled studies also provide data on the association between antidepressant drugs and suicidal ideation, attempts and fatalities. These include studies which: (a) suggest that electroconvulsive therapy may be more effective than antidepressant drugs in reducing the frequency of suicide attempts; (b) indicate that antidepressants may differ in their capacity to reduce the frequency of suicide attempts; (c) find that more overdose attempts were made by patients receiving maprotiline than placebo; and (d) suggest that fluoxetine may be associated with a greater risk of inducing *de novo* suicidal ideation.

Evidence suggests that antidepressants may vary by at least 15-fold in the number of fatal overdoses per million prescriptions. Estimated overdose proclivity rates were derived after adjusting the fatal toxicity data by the therapeutic index of the drug. These rates were very consistent between agents with the same pharmacological properties, and correlated well with known overdose risk rates for amitriptyline, mianserin and maprotiline. Estimated overdose proclivity rates suggest that the highly selective noradrenaline (norepinephrine) uptake inhibitors (desipramine, nortriptyline, maprotiline) may be associated with a greater risk for overdose than more mixed uptake inhibitors and monoamine oxidase inhibitors (MAOIs).

Antidepressants are not uniformly neutral in regard to suicidal ideation and attempts. Data clearly demonstrate that antidepressants ameliorate suicidal ideation more effectively than placebo in patients with depression. Although antidepressants diminish suicidal ideation in many recipients, about as many patients experience worsening suicidal ideation on active medication as they do on placebo. Furthermore, at least as many patients attempted suicide on fluoxetine and tricyclic antidepressants as on placebo, and more patients attempted to overdose on maprotiline than placebo. These observations suggest that antidepressants may redistribute suicide risk, attenuating risk in some patients who respond well, while possibly enhancing risk in others who respond more poorly. Sophisticated studies will need to be conducted to meaningfully explore this possibility.

Major depression is a recurrent debilitating illness, affecting about 6% of the general population (Weissman et al. 1988). The introduction of antidepressant drugs in the 1950s heralded a new era in the treatment of serious mood disorders, and these agents have provided countless patients with undeniable relief. Emerging data also suggest that antidepressant drugs, at an appropriate dose, offer the best hope for sustained recovery (Frank et al. 1990).

Despite their unassailable importance, antidepressants can produce serious adverse responses in some patients. Recent concerns have focused on the potential for some antidepressants to produce or exacerbate suicidal tendencies. The purpose of this article is to review available evidence suggesting that antidepressants can, in rare instances, amplify or induce suicidal ideation and impulses. Possible clinical and preclinical mechanisms are provided to explain how drugs may produce suicidal obsessions, or trigger self-destructive behaviours in susceptible patients. Clinically significant risk factors are also identified, to the extent that they are known.

Though this review focuses on adverse behavioural effects of antidepressants, we should state at the outset that the overwhelming preponderance of data indicate that these drugs are relatively safe and of unquestionable value. Although it is very important for clinicians and researchers to realise that although antidepressants may exacerbate suicidal tendencies in a small subset of patients, it is equally important that we remember that these drugs quell depression and ease suicidal thoughts in the majority of recipients.

1. Antidepressants and Suicidal Tendencies: Clinical Mechanisms

Two pathways have been postulated through which antidepressant drugs may exacerbate suicidal tendencies. In the first model, antidepressants

may energise suicidal patients to act on their impulses (Feuerstein & Jackisch 1980). In the second model, antidepressants may produce a paradoxical worsening of depressive symptoms, leading to the emergence of suicidal thoughts or actions (Damluji & Ferguson 1988). We believe that there are numerous other pathways through which antidepressants may also exacerbate suicidal tendencies.

In susceptible patients, antidepressants may produce a variety of neuropsychiatric states associated with suicidal ideation or behaviour. These states include akathisia, panic-anxiety, mania and insomnia. We also propose that certain antidepressants may produce, in vulnerable individuals, organic obsessive-compulsive reactions or organic borderline personality reactions, which may lead to suicidal obsessions or intense self-destructive impulses. Evidence supporting these assertions is summarised below.

1.1 Energising Role of Antidepressants

It is a well accepted clinical dictum that antidepressant drugs produce uneven temporal resolution of depressive symptoms. Thus, sedating antidepressants can sometimes produce immediate improvement in sleep quality, while symptoms of depressed mood and guilty ruminations may persist for weeks. Similarly, antidepressant drugs can sometimes stir depressed patients out of their lethargic, abulic, psychomotor retarded state without reversing their fundamental dysphoria. As a consequence, antidepressants may provide the energy to enable depressed patients to act on pre-existing suicidal plans or intentions (Feuerstein & Jackisch 1980). For this reason, depressed suicidal patients should be followed very closely during the early phase of treatment. Although antidepressants have not been formally compared regarding their potential to augment energy before reversing depressed mood, Feuerstein and Jackisch (1980) hypothesised that selective noradrenergic uptake inhibitors would [by directly enhancing noradrenergic neural transmission, and reciprocally inhibiting serotonin (5-hydroxytryptamine; 5-HT) neurotransmission] have a particularly strong proclivity to rapidly energise patients while leaving them dysphoric. This report was severely criticised by Montgomery and Pinder (1987), who presented data on the incidence of fatal overdoses with different antidepressants, and showed that single drug fatalities occurred most often in patients taking the mixed amine uptake inhibitors amitriptyline and dothiepin. However, emerging evidence demonstrating a disproportionately high incidence of fatal overdoses on desipramine, and a double-blind study by Rouillon et al. (1989) demonstrating a higher incidence of overdose attempts in patients receiving maprotiline versus placebo (reviewed below), has caused Montgomery to reverse his opinion (Montgomery & Bullock 1991). Unfortunately, comparable data on selective serotonin inhibitors are not yet available. In contrast to certain antidepressant drugs, electroconvulsive therapy (ECT) may attenuate suicidal ideation before it enhances energy (Rich et al. 1986). As reviewed below, some studies suggest that ECT may be more effective than medications in reducing the risk of suicide in depressed patients (Tanney 1986). The basic pharmacological properties of antidepressant drugs and their capacity for stimulation are summarised in table I.

1.2 Paradoxical Worsening of Depression

On balance, antidepressant medications are roughly equivalent in their capacity to treat depression (Baldessarini 1989), though they may differ in their spectrum of activity towards distinct depressive subtypes (Baldessarini 1989). In general, a given antidepressant will produce a clearly favourable clinical response in about 70% of recipients (Baldessarini 1989). Most of the remainder will show no significant effect, and a small percentage will worsen. Damluji and Ferguson (1988) estimated that about 1% of 800 patients treated in their practice showed a paradoxical response to antidepressants, with a marked worsening of depression, and *de novo* emergence of suicidal ideation. They describe 4 patients treated initially with desipramine who developed worsening depression, 2 with suicidal ideation emerging *de novo*. During a second medication trial, 2 of these patients again

Table I. Adverse effect incidence for various antidepressants. Every attempt was made to express incidence quantitatively as drugs *vs* placebo or drug alone. Qualitative evaluation was used only when quantitative rates could not be found. Adverse effect incidence based on Physicians' Desk Reference (1992) plus the following: Dominguez et al. (1985); Garland et al. (1988); Greenblatt et al. (1962); Hoc (1982); Larsen & Relaelsen (1980); Mallya et al. (1992); Peck et al. (1983); Rack & Vaddadi (1975); Reimherr et al. (1990); Robinson et al. (1978, 1982); Stark & Hardison (1985); Vauterin & Bazot (1979); White et al. (1984)

Antidepressant	NE : SER ratio[a]	Anticholinergic ratio[b]	Seizure risk	Agitation or excitement (%)	Nervousness or anxiety (%)	Insomnia (%)	Sedation or drowsiness (%)	Weakness or fatigue (%)
Monoamine uptake inhibitors								
Noradrenaline (norepinephrine) >> serotonin								
Desipramine	378 : 1	1 : 220	Infrequent	Frequent	**	Infrequent	*	**
Maprotiline	446 : 1	1 : 77	3/1000	2	6	2	*	4
Nortriptyline	65 : 1	1 : 38	Infrequent	10 *vs* 13	**	11 *vs* 11	*	**
Protriptyline	289 : 1	1 : 26	Infrequent	10-25	***	Frequent	*	**
Noradrenaline > serotonin								
Amitriptyline	3 : 1	1 : 0.8	0.5/1000	15 *vs* 11	*	9 *vs* 11	41 *vs* 12	24 *vs* 10
Dothiepin	3 : 1	1 : 0.7	Infrequent	6	*	3	****	***
Doxepin	14 : 1	1 : 4	Infrequent	2	<1	2	***	****
Imipramine	3 : 1	1 : 7	1-6/1000	17	18 *vs* 15	10 *vs* 8	***	13
Serotonin > noradrenaline								
Clomipramine	1 : 8	1 : 7	15/1000	3 *vs* <1	18 *vs* 2	25 *vs* 15	54 *vs* 16	39 *vs* 18
Serotonin >> noradrenaline								
Fluoxetine	1 : 23	1 : 167	2/1000	Frequent	15 *vs* 9	14 *vs* 7	2 *vs* 1	4 *vs* 1
Fluvoxamine	1 : 71	1 : 1692	Infrequent	14 *vs* 3	29 *vs* 14	56 *vs* 29	4	50 *vs* 21
Sertraline	1 : >100	1 : 3429	<1/1000	6 *vs* 4	3 *vs* 2	16 *vs* 9	13 *vs* 6	11 *vs* 8
Atypicals (weak uptake inhibitors)								
Amfebutamone (bupropion)	7 : 1	1 : 76	4/1000	32 *vs* 22	3 *vs* 1	19 *vs* 16	20 *vs* 20	3 *vs* 3
Mianserin	55 : 1	1 : 117	Infrequent	7	*	2	44	***
Trazodone	1 : 26	1 : 46 286	Rare	3 *vs* 4	10 *vs* 9	8 *vs* 11	33 *vs* 15	8 *vs* 3
Trimipramine	5 : 1	1 : 2	Infrequent	Infrequent	9	4	***	***
Monoamine oxidase inhibitors								
Isocarboxazid			Rare	5	**	45	**	21
Phenelzine			Rare	8	11	54	***	19
Tranylcypromine			Rare	24 *vs* 13	**	54 *vs* 11	**	***

a NE : SER ratio = inhibitor constant (K_i) for noradrenaline uptake/K_i for serotonin uptake. Data derived largely from Richelson & Pfenning (1984).

b Anticholinergic ratio = potency at muscarinic site *vs* potency at site of primary pharmacological action (higher ratio indicates lower anticholinergic effect). Data derived largely from Richelson & Nelson (1984) and Wander et al. (1986).

Symbols: * = very low; ** = low; *** = moderate; **** = high; rare = <1/1000; infrequent = >1/1000 but <1/100; frequent = >1/100

developed worsening depression during amoxapine treatment, while the remainder also worsened, with recurrent suicidal ideation, while receiving trazodone or nortriptyline. Three patients eventually responded to fluoxetine and one to ECT therapy. Damluji and Ferguson's (1988) report indicates that patients may respond paradoxically to more than one antidepressant. Recently, Creaney et al. (1991) described two patients whose condition worsened during treatment with fluoxetine. The first patient experienced the same dissociative symptoms during rechallenge with fluvoxamine. The second patient developed akathisia and violent self-destructive thoughts on fluoxetine, and developed intolerable akathisia on imipramine, but responded favourably to phenelzine.

Hoover (1990) reported a single case of a 29-year-old man with atypical depression and panic disorder with no history of suicidal ideation, who developed suicidal ideation on fluoxetine, and made a suicide attempt following rechallenge with fluoxetine. The patient responded well to ECT. However, shortly thereafter, the patient developed suicidal ideation on imipramine, which led Hoover (1991) to believe that suicidality was more likely a new manifestation of the patient's depression rather than a consequence of fluoxetine. Massand and Dewan (1991) pointed out the alternative explanation that Hoover's patient could have developed treatment-related suicidal ideation on both agents. Gualtieri (1991) argues that fluoxetine and other serotonin uptake inhibitors may be particularly prone to produce 'bilaterally-symmetric' adverse effects (e.g. anorexia *vs* hyperphagia, diminished aggression *vs* self-injurious behaviour, anorgasmia *vs* spontaneous orgasms, hypersomnia *vs* insomnia), due to the complexity of the serotonin system.

In double-blind, placebo-controlled studies, antidepressant drugs have also been observed to produce frequent paradoxical reactions in patients with borderline personality disorder. In an important study, Soloff et al. (1986) found that nearly 50% of borderline personality disorder patients treated with amitriptyline became progressively more depressed with treatment, and showed worsening behavioural control, aggressivity, and increased suicidality. In contrast, Cowdry and Gardner (1988) and Liebowitz and Klein (1981) found that borderline patients (or a closely allied group of hysteroid dysphorics) responded favourably to monoamine oxidase inhibitors (MAOIs) without paradoxical reactions. Recent studies also suggest that borderline patients may respond favourably to fluoxetine (Cornelius et al. 1991). These observations suggest that specific patient populations may respond differently to various classes of antidepressant drugs. It should also be mentioned that a significant percentage of borderline personality disorder patients have been reported to develop worsening of depression on carbamazepine (Cowdry & Gardner 1988) and thioridazine (Teicher et al. 1989), and to experience paradoxical rage reactions (resulting in behavioural dyscontrol and violence) on alprazolam (Gardner & Cowdry 1985).

1.3 Akathisia

Akathisia is an intense multifaceted state of inner agitation and restlessness that is often provoked by antipsychotic drugs (Van Putten 1975). Akathisia frequently produces severe internal distress, and has been reported to have resulted in suicidal states in some patients (Drake & Ehrlich 1985; Schutte 1985; Shaw et al. 1986; Shear et al. 1983), or to have unleashed aggressive behaviours (Crowner 1990; Herrera et al. 1988; Keckich 1978; Schutte 1985). Although akathisia is primarily observed in patients taking antipsychotic drugs, recent reports indicate that antidepressants may also produce this adverse effect (Krishnan et al. 1984; Lipinski et al. 1989; Zubenko et al. 1987), and indicate that patients with depression may be more vulnerable to the emergence of akathisia than patients with schizophrenia or mania (Gardos et al. 1992).

Recently, Wirshing et al. (1991) described 5 patients who developed prominent akathisia and suicidal ideation during treatment with fluoxetine. Resolution of the akathisia resulted in cessation of the suicidal thinking. Rothschild and Locke (1991) described 3 patients who had made serious suicide attempts during fluoxetine treatment, who were re-

challenged with fluoxetine. All 3 developed severe akathisia during rechallenge, stating that the emergence of akathisia made them feel suicidal and that the akathisia had precipitated their prior suicide attempt. Akathisia and suicidal ideation abated on the discontinuation of the fluoxetine or the addition of propranolol (Rothschild & Locke 1991).

Antidepressant drugs have not been ranked in their capacity to induce akathisia. Generally, tricyclic antidepressants (TCAs) produce a form of 'jitteriness' in susceptible patients, which is probably a mild form of akathisia. It is our impression that more serious akathetic states seem to occur predominantly in patients receiving fluoxetine or other high potency serotonin uptake inhibitors (e.g. clomipramine), and in patients receiving amoxapine, which has direct dopamine antagonist properties.

1.4 Panic-Anxiety

Panic attacks are recurrent episodes of unprovoked intense paroxysmal fear that are accompanied by symptoms such as palpitations, chest pain, shortness of breath, faintness and dissociation. These attacks have been recognised in epidemiological investigations as a predisposing factor in suicide (Coryell et al. 1982, 1986), equal to depression in life-time risk (Johnson et al. 1990; Weissman et al. 1989), and a more powerful determinant of short term risk (Fawcett et al. 1990), though this finding has not been confirmed in a recent clinical sample (Beck et al. 1991). Panic attacks have also been linked to the emergence of anger and aggressive behaviours (Fava et al. 1990; George et al. 1989; Korn et al. 1992). Antidepressant drugs and high potency benzodiazepines are treatments of choice for panic (Aronson 1987; Balestrieri et al. 1989; Deltito et al. 1991; Liebowitz et al. 1990; Svebak et al. 1990). A number of studies have also demonstrated antipanic efficacy of high potency serotonin uptake inhibitors including clomipramine (Gloger et al. 1981, 1989), zimeldine (Evans et al. 1986), fluoxetine (Gorman et al. 1987; Schneier et al. 1990) and fluvoxamine (Den Boer & Westenberg 1988; Servant et al. 1990). However, some antidepressant drugs and anxiolytics appear to be ineffective. These include maprotiline (Den Boer & Westenberg 1988), trazodone (Charney et al. 1986) and the nonbenzodiazepine anxiolytic buspirone (Sheehan et al. 1990).

Most studies suggest that patients with panic disorder respond to lower antidepressant doses than patients with major depression, and that they are substantially more vulnerable to antidepressant adverse effects (Aronson 1987; Gloger et al. 1989; Mavissakalian & Perel 1989; Schneier et al. 1990; Sveback et al. 1990; Sweeney et al. 1983-1984). In particular, they seem to be very susceptible to development of 'jitteriness' (Liegghio et al. 1988; Pohl et al. 1988), which may be a manifestation of akathisia (Zubenko et al. 1987). It also appears that the high potency serotonin uptake inhibitors fluoxetine and fluvoxamine, at usual antidepressant doses, can initially exacerbate panic symptoms in some susceptible patients (Den Boer & Westenberg 1988; Gorman et al. 1987; Schneier et al. 1990), and induction of nervousness and anxiety is the major reason for discontinuation of fluoxetine in clinical trials. We suspect that precipitation of panic attacks, or worsening of panic symptoms, may be another mechanism through which antidepressants enhance suicidal tendencies in a relatively small subset of patients. Selective, high potency serotonin uptake inhibitors, prescribed even at common antidepressant doses, may pose the greatest risk for susceptible patients. In this regard, it should be noted that 2 of 16 panic disorder patients developed depression and suicidal ideation during treatment with fluoxetine at conventional dosage (Gorman et al. 1987). For patients with a history of panic attacks, even if rare or currently inactive, it may be prudent to begin treatment with lower than usual doses.

1.5 Manic or Mixed Manic and Depressive States

Mania is a state characterised by euphoria, excessive energy, decreased need for sleep, reckless behaviour, increased speech and poor judgement. Several studies suggest that TCAs and MAOIs sub-

stantially increase the rate at which bipolar patients switch from depression into mania, or shorten their cycle length (Goodwin & Jamison 1990). Although suicide attempts may be relatively infrequent during pure manic episodes, impulsivity and aggression exist as important clinical features (Platman et al. 1969). Dysphoric and mixed states are associated with a significantly higher risk of suicide. Winokur and colleagues (1969) reported that the rate of suicide threats and attempts was 13% in patients suffering from post-manic depressive episodes, and that 43% of all patients in mixed manic and depressive states were so affected. Indeed, Jameison (1936) found the mixed state to be the most dangerous clinical phase for suicide risk. Theories surrounding lethality during mixed states suggest that the combination of depressive symptoms, mental alertness, heightened energy and increased impulsivity present a dangerous and volatile combination leading to an unacceptably high likelihood of suicide (Goodwin & Jamison 1990; Jameison 1936). Schweizer et al. (1988) have also postulated that a drug-induced swing from severe depression into mania or hypomania, followed by a switch back into depression, may be a particularly strong trigger for impulsive suicidal acts.

No valid systematic data exist on the relative propensity of different antidepressant agents to induce mixed states, although numerous studies have investigated the development of mania in patients treated with antidepressants. Early studies suggested a 10% incidence of mania in patients treated with either TCAs or MAOIs (Bunney et al. 1972). Subsequent studies have shown that mania or hypomania emerge in 3 to 70% of all patients treated with antidepressants (usually TCAs) [Goodwin & Jamison 1990]. Others have argued that the incidence of antidepressant-induced mania is not a consequence of treatment, but instead reflects the natural course of the illness (Angst 1985; Lewis & Winokur 1982), though these studies appear particularly flawed (Goodwin & Jamison 1990). Newer non-TCAs and anxiolytics, including alprazolam (Arana et al. 1985) and fluoxetine (Chouinard & Steiner 1986; Lebegue 1987; Nakra et al. 1989), have been reported to induce manic episodes as well. It is also unclear how effective lithium is in preventing drug-induced manias or mixed states. A limited amount of data suggest that it may be partially, but incompletely, effective (Prien et al. 1984). However, it is also known that the addition of lithium to antidepressants can sometimes precipitate manic reactions (Louie & Meltzer 1984; Price et al. 1984). Great care should be employed in the pharmacological treatment of patients with known or suspected bipolar illness, and these patients should be closely monitored for the emergence of mixed or manic reactions. The emergence of mania can markedly enhance risk for violent aggressive behaviour. Drug-induced precipitation of a mixed manic and depressive state can seriously augment suicide risk.

1.6 Insomnia or Disturbances in Sleep Architecture

Many of the classic papers examining symptoms associated with suicidal acts underscore the importance of insomnia as a risk factor. Jameison and Wall (1933) in a study of patients who eventually committed suicide indicated that one of the most outstanding features of their clinical picture was sleeplessness, which was a constant worry for them, and it led to much anxiety and despair. Slater and Roth (1969) stressed that one of the major clinical risk factors for suicide was severe insomnia, particularly if there was a persistent disproportionate concern about it. Barraclough et al. (1974) in an examination of 100 cases of suicide found that the most prevalent overall symptom was insomnia. Indeed, 76% of this group suffered from insomnia, and 64% were taking hypnotic drugs. Motto (1975) wrote: 'Do not underestimate the critical importance of sleep. A frantic effort to obtain relief from insomnia often triggers a drug overdose'. Thus, insomnia may represent an important risk factor. Many antidepressants are sedating, and facilitate initiation of sleep. Agents that are particularly noteworthy in this regard include amitriptyline, doxepin, trimipramine and trazodone.

Other antidepressants, particularly those that are

stimulating for some patients, may interfere with sleep initiation. These include protriptyline, desipramine, tranylcypromine, isocarboxazid, fluoxetine and amfebutamone (bupropion). The more hypnotic agents may therefore decrease suicide risk in some patients if they attenuate insomnia, whereas the more arousing agents can potentially enhance risk, if they induce insomnia. However, it is likely that patients planning to overdose would probably prefer to select a highly sedating agent. Thus, it is conceivable that patients may have their suicidal state enhanced by a stimulating drug (if it causes profound insomnia), only to use a sedating drug (or drug combination) in an overdose attempt.

It is also possible that there may be a relationship between alterations in sleep architecture and suicidal tendencies. Harvey (1980) wrote: '[S]trong suppression of stage 4 [*sleep*] may cause the emergence of day terrors or of suicidal ideation'. However, we could identify no journal articles that have directly examined this hypothesis. Recently, Sabo et al. (1991) conducted a retrospective study of the sleep EEG in patients with major depression with and without a history of suicide attempts versus normal controls. Data from carefully matched groupings were analysed. At the time of the sleep study, patients with a history of suicide attempts were no more suicidal than depressed patients without such a history. Thus, this study focused on possible trait differences rather than state differences. Suicide attempters, compared with depressed non-attempters and controls, had longer sleep latencies, lower sleep efficiencies and fewer late-night delta counts. Moreover, attempters had a significant increase in the number of rapid eye movements, as indicated both by visual inspection (65% increase, $p < 0.01$), and by period analysis (98% increase, $p < 0.01$). Sabo et al. (1991) hypothesised that these differences in sleep architecture may reflect alterations in serotonin function. Keck et al. (1991) recently published preliminary data on the sleep architecture of patients experiencing worsening insomnia or new-onset insomnia while on fluoxetine. Although this study was limited by small sample size ($n = 7$) and lack of pretreatment sleep studies, they reported that fluoxetine appeared to produce a very dramatic increase in rapid eye movement (REM) activity that they had not observed with any other class of psychotropic drugs, and that these subjects had numerous rapid eye movements, even during non-REM sleep stages. They also reported a significant reduction in delta sleep compared with healthy controls. Thus, to some extent, the disturbances in sleep architecture of depressed patients experiencing insomnia on fluoxetine may have some similarities to the sleep architecture abnormalities of unmedicated depressed patients with a history of suicide attempts (Sabo et al. 1991).

1.7 Obsessive Suicidal Preoccupation

Recently, concerns have been raised that the new antidepressant fluoxetine can induce obsessive suicidal ideation. Much of the concern stems from a series of case reports published by Teicher et al. (1990), who described 6 complicated patients with major depression who developed violent suicidal preoccupations during treatment with fluoxetine. Five depressed outpatients and 1 inpatient, 19 to 62 years of age, developed intense suicidal thoughts a mean of 26 days (range 12 to 50 days) after initiation of fluoxetine treatment. This state was more intense, obsessive and violent than anything they had previously experienced. One patient had no prior suicidal ideation, and only 3 patients had ever made previous attempts or gestures. These intense self-destructive thoughts persisted, and even worsened temporarily, after discontinuation of fluoxetine treatment. They faded in intensity an average of 27 days (range 3 to 49 days) later, but they did not fully abate in most patients until a mean of 87 days (range 60 to 106 days) after cessation of treatment. Four patients received relatively high daily doses of fluoxetine (60 to 80mg), but 2 patients received only 20 to 40mg. Two patients developed suicidal ideation while receiving only fluoxetine. The remainder were taking a variety of other medications.

All patients had previously been treated with MAOIs, and for 3 cases, an MAOI had been the

last treatment before fluoxetine. Resumption of MAOI treatment (after at least a 6-week washout period) appeared to result in rapid abatement of persistent suicidal ideation in the 3 cases in which this was tried.

In no case was there evidence that strong pre-existing self-destructive urges were activated and energised by fluoxetine. No patient was actively suicidal at the time when fluoxetine treatment began. Rather, all were hopeful and optimistic about the potential benefits of treatment, and the strong obsessive suicidal thoughts apparently emerged after weeks or months of treatment. In 4 patients, these thoughts were accompanied by abject acceptance and detachment. Two patients tried to conceal their suicidal feelings and impulses and to continue fluoxetine treatment, believing that the drug would eventually enable them to successfully kill themselves. These thoughts were uncharacteristic in that they were more intense, obsessive and violent than anything these patients had previously experienced. They were obsessive in the sense that they were recurrent, persistent and intrusive. These thoughts emerged without reason, but were the patients' own thoughts. It was also remarkable how violent they were. Two patients fantasised, for the first time, about killing themselves with a gun, and 1 patient actually placed a loaded gun to her head.

Similar reactions have occurred in a few patients with more typical depressions and with simpler treatment histories. Dasgupta (1990) described the case of a 38-year-old woman treated with fluoxetine 20 mg/day for depression secondary to hysterectomy. After 4 weeks' treatment, she developed worsening symptoms of depression, intense suicidal preoccupation and violent thoughts of killing herself, leading to a suicide attempt. Her depression and suicidal ideation decreased 2 to 3 days after discontinuing fluoxetine, and the patient was totally free of these symptoms 4 days after discontinuation. Masand et al. (1991) described 2 additional patients who developed violent suicidal ideation within 3 to 10 days of initiation of treatment with fluoxetine. Both patients suffered from major depression, one with concurrent bulimia; however, neither showed any evidence of personality disorder or had a history of suicidal ideation, gestures, mania or hypomania. Suicidal ideation rapidly disappeared within a week of discontinuation. Creaney et al. (1991) also described 2 cases of suicidal ideation associated with fluoxetine treatment. One of these cases displayed obsessive suicidal preoccupation, and eventually showed a favourable response to an MAOI. Unlike the majority of cases reported by Teicher et al. (1990), this patient had a simpler treatment history, and developed these symptoms on a daily fluoxetine dose of only 20mg.

These case reports have generated considerable interest and criticism. Some critics reject the entire phenomenon as it is based entirely on case report data. Others argue that the emergence of an intense obsessive suicidal state must be a manifestation of the patient's underlying depression. Still others reject the hypothesis because they believe that it is not possible for a drug to produce specific thoughts. We would like to clarify that we are not arguing that the drug produces a specific thought, but rather that it interferes with normal thought processes. Our hypothesis is not that drugs cause patients to specifically become obsessive about suicide, but rather that they produce a drug-induced obsessive state in which thoughts may focus on suicide, death or self-destructive acts. The following new case history describes the development of these symptoms in a patient *without* major depression, and strongly suggests that this reaction is a form of drug-induced obsessive-compulsive state, rather than an exacerbation of depression.

Case 7 was a 28-year-old woman with a 4-year history of chronic fatigue disorder. She had classic symptoms of chronic fatigue, including lymphadenopathy, persistent fever of unknown aetiology, myalgia with trigger points, anergic response to multiple antigens and profound fatigue that often left her bedridden. Her evaluation also included negative lymph node biopsy, lumbar puncture, bone marrow aspirate, colonoscopy, whole body computerised tomography (CT) scan, bone scans and normal evoked potential responses. Additional positive findings included an abnormal EEG with independent irregular slowing exacerbated by hy-

perventilation, slightly diminished coordination and balance, and mildly abnormal neuropsychological testing indicating a significant problem with calculations that was probably not present when she was younger. She also had an abnormally low haptoglobin level and hepatomegaly. Curiously, she was felt to be free of depressive symptoms. Over the course of this disorder she saw 2 psychiatrists for consultations (largely as part of disability evaluations), and neither found any evidence for underlying depression or any other psychiatric disorder. Indeed, she was in some ways quite happy. She had accommodated to her physical problems and was planning to marry. She agreed to undergo a course of treatment with fluoxetine for her chronic fatigue syndrome after it was recommended by 2 specialists. Her hope was to experience enough relief from her fatigue so she could go through with wedding plans and could consider raising a family. Prior to these psychiatric consultations she had never seen a mental health professional and had never received treatment with any psychotropic drugs. She had no history of alcohol or substance abuse.

Fluoxetine was initiated at a dosage of 10 mg/day for 4 days, and was increased thereafter to a daily dose of 20mg. Ten to 14 days later she experienced marked loss of appetite, constipation, tinnitus and a 'full' feeling in her head. Her energy level did start to improve and myalgia pains abated. Three weeks after starting fluoxetine she experienced a passing violent thought about harming her father. She was able to easily dismiss this thought. Four days later she awoke in the middle of the night hearing her own voice yelling at her to get up and stab her father. Another voice, also her own, was telling her not to. The next morning she remembered the event as terribly bizarre, but felt normal during the day. The following night the same events occurred. However, the following day she could not get these thoughts off her mind. She thought about stabbing her father with a knife, and saw violent images. She found the obsession to be all-consuming, and she knew that something was terribly wrong. Although fluoxetine had markedly attenuated her chronic fatigue symptoms, she stopped this medication 5 days later after a total of 31 days of treatment.

Nevertheless, her violent thoughts continued to evolve. She became obsessed about killing other people she loved, and within a few days she ruminated obsessively about killing herself. During this period she also felt emotionally disconnected, was largely apathetic and was no longer able to feel love. These symptoms continued for 6 months and only gradually started to abate thereafter. She maintained a barely discernible concentration of norfluoxetine in her blood (≈6 ng/ml 6 months after last dose). Approximately 2 months after this final blood measure, while receiving treatment with valproic acid, she experienced the complete return of her chronic fatigue syndrome and cessation of these obsessive thoughts. She remains quite frightened that they may return, however, and has significant anticipatory anxiety regarding events and objects that used to trigger these obsessions.

Papp and Gorman (1990) formulated an important hypothesis that emergence of intense suicidal obsessions on fluoxetine may represent a form of 'serotonergic syndrome' in susceptible patients. They observed that a rapid increase in fluoxetine dose in obsessive-compulsive disorder (OCD) patients produced a transient worsening of obsessions and compulsions (Liebowitz et al. 1989), and believe that a sudden increase in serotonin neurotransmission may be responsible (Papp & Gorman 1990). Serotonin is a key neurotransmitter in the behavioural inhibitory system (Depue & Spoont 1986), and some authorities have postulated that OCD may be due to excess serotonin neurotransmission in frontal cortex projections (Insel et al. 1990), and that anti-obsessional drugs work, after a lag period, by diminishing serotonin neurotransmission through inhibition of firing, receptor downregulation or desensitisation, or impaired serotonin release (Gardier & Wurtman 1991; Insel et al. 1990; Sarkissian et al. 1990; Wampler et al. 1987). We theorise that the serotonin system plays a pivotal role in enabling us to immediately dismiss normally fleeting and transient suicidal or homicidal thoughts from consciousness, and believe that it helps prevent us from acting on our aggressive

impulses (Depue & Spoont 1986). Excessive augmentation in serotonin neurotransmission may render patients unable to dismiss these thoughts, leading to ego-alien obsessions. On the other hand, excessive inhibition of serotonin neurotransmission may cause patients to impulsively act on aggressive thoughts in a manner that is clearly out of character (Teicher et al. 1991b).

Very recently there has emerged some independent confirmation of fluoxetine's potential to induce typical obsessive-compulsive symptoms in patients with major depression but with no personal or family history for OCD, Tourette's syndrome or tics. A brief letter by Dorval and Meinzer (1991) describes 3 cases of depressed women who developed classical, nonviolent, obsessive-compulsive symptoms (e.g. counting rituals) within 4 to 5 weeks of initiation of treatment with fluoxetine. These symptoms fully abated within 2 to 4 weeks after fluoxetine was discontinued.

The potential vulnerability of adolescents with obsessive symptoms to the effects of fluoxetine was highlighted in a recent report by King et al. (1991). They observed the emergence of intense suicidal ideation and self-destructive behaviour in 6 patients receiving fluoxetine for OCD or Tourette's disorder with obsessive symptoms. Adverse reactions emerged 1 to 6 months or more after the initiation of treatment and persisted up to 1 month after discontinuation. Three patients made suicide attempts or gestures (1 involving a massive overdose), and 3 manifested persistent, driven self-injurious behaviour requiring intensive intervention (restraint, one-to-one nursing care). The emergence of this behaviour was sufficiently severe to require hospitalisation in 4 patients. Additional subjects also developed uncharacteristic aggressive behaviour. Two of the 6 patients received a second trial of fluoxetine which again led to reappearance of suicidal ideation. Koizumi (1991) independently reported the same phenomenon in another adolescent with OCD. On the other hand, Beasley et al. (1992) reported no statistical association between the use of fluoxetine and the emergence of substantial suicidal ideation in a reanalysis of Eli Lilly-sponsored clinical trials in OCD (see below).

As noted above, most of the patients reported by Teicher et al. (1990) had received relatively high doses of fluoxetine. The emergence of suicidal behaviours may well be a dose-dependent phenomenon. Brewerton (1991) suggested this possibility in a recent review, and reviewed the fluoxetine clinical trial data, which provided some support. First, Brewerton (1991) found that Wernicke et al. (1987), in the only comprehensive fixed-dose comparison study, reported that 60mg doses of fluoxetine produced an initial worsening of symptoms compared with placebo. In this study, 1 of 105 patients on the 60mg dose made a suicide attempt compared with no patients on 40mg (n = 103), 20mg (n = 100) or placebo (n = 48). Muijen et al. (1988) reported that 2 of 26 depressed patients made overdose attempts during the first 2 weeks of treatment on another rapid fluoxetine titration schedule (40 mg/day in week 1, 60 mg/day in week 2). Levine et al. (1987) also reported that 7% of 59 non-depressed obese subjects developed depression following rapid titration of fluoxetine to a daily dose of 80mg. Thus, use of lower doses may enhance safety, and some studies suggest that daily doses of 20mg may be preferable for the treatment of major depression (Altamura et al. 1988). Finally, it should be noted that Fava and Rosenbaum (1992) have noted (without elaboration) the emergence of an obsessive preoccupation with suicide or self-directed violence in 2 patients taking antidepressants other than fluoxetine.

1.8 Borderline States or Hostility

Borderline personality disorder is a serious psychiatric disturbance generally characterised by intense unstable interpersonal relationships, affective instability, aggression, frequent suicidal thoughts or attempts and self-destructive behaviour. Although this is often considered to be the result of abnormal personality development, there is increasing recognition that these symptoms are highly suggestive of a state of serotonin dysregulation (Cornelius et al. 1991), either through diminished serotonin release or diminished receptor response (Coccarro et al. 1989). As reviewed above, these

patients often respond favourably to treatment with MAOIs or fluoxetine (Cornelius et al. 1991; Cowdry & Gardner 1988), but a substantial percentage may show paradoxical worsening of hostility and self-destruction on amitriptyline (Soloff et al. 1986) and alprazolam (Gardner & Cowdry 1985).

We postulate that certain patients who do *not* suffer from borderline personality disorder may have drug-induced borderline reactions that include the emergence of uncharacteristic aggression, self-mutilation and suicide. One of the 6 patients described by Teicher et al. (1990) displayed this type of reaction. During the course of treatment she developed an uncontrollable urge to mutilate herself, and needed to be physically restrained for extended periods of time. Another example is the case of Rhonda Hala, the first individual to file suit against the manufacturer of fluoxetine. This woman enjoyed a happy marriage, had well developed and well behaved teenage children, a stable career and many close friends. She had no known history of depression or borderline personality, and had never seen a mental health professional. She became depressed and anxious after she suffered a severe back injury which was unresponsive to bedrest and treatment with nonsteroidal anti-inflammatories. She was initially treated for anxiety and depression with fluoxetine and buspirone. Shortly thereafter, for the first time in her life, she purposefully and intentionally cut herself. Fluoxetine was discontinued, and she was treated with fluphenazine (briefly), alprazolam and imipramine, which produced unacceptable physical adverse effects. Due to nonresponse to the other agents, fluoxetine was restarted. Two weeks later she again started to cut herself. Over time her daily dose was increased to 60mg, and the cutting behaviour became incessant, eventually requiring plastic surgery. Over her course of treatment she made several serious suicide attempts and assaulted her psychiatrist many times. This state persisted for about 18 months until her psychiatrist read about this possible adverse reaction and stopped the fluoxetine. About 4 weeks later the suicidal thoughts and self-destructive behaviour fully abated, without recurrence.

It is interesting to note that current biological research suggests that patients with borderline personality disorders have diminished release of serotonin or diminished serotonin receptor sensitivity (Coccarro et al. 1989). Thus, medications that augment the synaptic action of serotonin (e.g. serotonin uptake inhibitors, MAOIs) may be useful in the treatment of patients with this disorder. On the other hand, evidence suggests that serotonin uptake inhibitors can diminish serotonin receptor sensitivity and release in patients with OCD, who probably have excessive serotonin neurotransmission (Insel et al. 1990). Animal studies also suggest that fluoxetine can rapidly attenuate drug-induced or depolarisation-induced release of serotonin in normal rats (Gardier & Wurtman 1991; Sarkissian et al. 1990), or can, in some instances, down-regulate serotonin receptors or diminish response to serotonin agonists (Wampler et al. 1987; Wong et al. 1985). Thus, depending on the basal state of serotonin release, this agent may possibly augment serotonin neurotransmission in some subjects and may diminish it in others. Furthermore, these effects may change over time and may vary with dose.

In terms of the emergence of self-destructive or aggressive behaviour in depressed patients, it is interesting to note that these symptoms are not related to the patient's degree of depression, but to the degree that they feel angry and hostile (Yesavage 1983). Psychotherapeutic drugs have not been well evaluated for their effects on anger and hostility, though it has been reported that some antidepressants, notably imipramine, can increase anger and hostility, particularly at therapeutic doses (Natale 1979; Pallmeyer & Petti 1979).

1.9 Alterations in EEG Activity

Most current research on the biological basis for suicidal behaviour has focused on biogenic amines, particularly serotonin. However, one of the earliest pioneering studies on physiological determinants of suicide reported a strong positive association between paroxysmal EEG disturbances and suicidal ideation, suicidal ideation and attempts, and assaultive-destructive behaviour (Struve et al. 1972). The authors hypothesised that the paroxysmal EEG

disturbance did not directly create the suicidal ideation, but may have led to an enhanced vulnerability to impairments in impulse control and planning (ability to reject suicidal thoughts). Downs et al. (1991) raised the possibility that many of the patients reported by Teicher et al. (1990) who developed suicidal thoughts on fluoxetine had limbic system dysfunction. Additional information published by Teicher et al. (1991a) revealed that 5 of the 6 reported cases had abnormal EEG studies, and 3 had abnormal magnetic resonance image (MRI) or CT scans. It is certainly possible that patients with EEG and limbic system abnormalities may be more susceptible to adverse responses to antidepressants. It is also true that antidepressants can induce EEG disturbances and can precipitate seizures. It is even conceivable that by inducing EEG abnormalities, antidepressants may enhance suicidal tendencies in some patients. It has been reported in the neurological literature that the risk of completed suicide is 4 to 5 times greater in patients with epilepsy than in non-epileptic patients, and that the risk in patients with temporal lobe epilepsy may be 25 times greater (Barraclough 1981; Matthew & Barabas 1981). As many as one-third of all patients with epilepsy have attempted suicide at some point (Delay et al. 1957; Jensen 1975). This risk is far greater for epileptics than for other medical patients with comparable degrees of handicap or disability (Mendez et al. 1986). Recently, Mendez et al. (1989) have provided data that this risk may be related to interictal psychopathological changes, particularly the high prevalence of borderline personality disorder. The relative propensity for various antidepressants to provoke seizures is reported in table I.

2. *Epidemiological and Controlled Studies*

Relatively few studies have provided either large scale epidemiological or controlled data on the emergence of suicidal ideation, frequency of suicide attempts or number of completed suicides during treatment with antidepressants. Some authors have assumed that antidepressants are neutral in terms of their effect on suicidal ideation, whereas other authors have speculated that some antidepressants are more effective in suppressing suicidal ideation; however, researchers have only rarely considered the possibility that antidepressants could enhance suicidal ideation. Review of the available literature suggests that antidepressants may differ in their effects on suicidal ideation, attempts and fatalities. Some data even point to the possibility that certain antidepressant drugs may produce a greater incidence of suicide attempts than no treatment or placebo.

2.1 ECT, Antidepressants and Placebo

In a very interesting study, Avery and Winokur (1978) examined the rate of attempted suicide during hospitalisation and for 6 months following discharge in depressed patients treated with ECT, antidepressants or no somatic treatment. During this entire period only 0.6% (2 of 317) of hospital cases who actually received ECT made suicide attempts compared with 6.8% (5 of 74) of hospitalised cases who received adequate antidepressant doses, 4.2% (6 of 142) of cases who received inadequate antidepressant doses and 4.0% (3 of 75) of patients who received neither ECT nor antidepressants. Overall, patients who received antidepressants in adequate doses were 10-times more likely to have made suicide attempts than patients who had received ECT (without or without antidepressants; $p = 0.003$).

In cases with known previous suicide attempts, the incidence of new attempts was 0.0% (0 of 49) for the group that received ECT. In contrast, 7.1% (1 of 14) of cases receiving adequate antidepressant doses, 11.8% (4 of 34) of cases receiving inadequate antidepressant doses and 9.1% (2 of 22) receiving neither treatment made suicide attempts. This observation suggests that ECT may be more effective than antidepressants in diminishing suicide risk, and that antidepressant drugs may exert relatively little protection compared with no somatic treatment. Finally, in patients without any known prior history of suicide attempts, 0.7% (2 of 268) of individuals who had received ECT made suicide attempts compared with 1.9% (1 of 53) of patients

receiving neither treatment. 1.9% (2 of 108) of cases receiving inadequate antidepressant doses, and 6.7% (4 of 60) of cases receiving adequate doses. Although this latter difference could have occurred by chance, it raises the possibility that 'adequate' antidepressant treatment in a low-risk patient population may paradoxically enhance suicide risk.

A majority of available reports also indicate that ECT may be more effective than conventional antidepressants in reducing the number of suicide attempts or fatalities. Greenblatt et al. (1962) in a study comparing random assignment of ECT (n = 28) with 1 of 3 antidepressant drugs (imipramine, phenelzine, isocarboxazid: n = 100), reported that 3 of the patients in the drug treatment group developed worsening depression with suicidal ideation, and needed to have their treatment switched to ECT. Ziskind et al. (1945) reported that in a mixed group of patients with affective psychosis, involutional melancholia and manic-depressive depression, during a follow-up period of 3.3 years, 8.3% of the untreated patients (n = 109) committed suicide compared with 1.1% who received ECT (n = 88). Huston and Locher (1948a) reported a suicide rate of 13% for patients with involutional melancholic psychosis (n = 93) who did not receive treatment, compared with a 1.6% rate for those treated with ECT (n = 61). Huston and Locher (1948b) also reported that 7.5% (n = 80) of untreated patients with manic-depressive depression committed suicide compared with only 1.4% of those who received ECT (n = 74). Unfortunately, in both of these studies the follow-up period was significantly longer for the untreated group (6.5 to 6.8 years) than the ECT group (3 years), though 78% of the untreated patients who successfully committed suicide did so within 2 years. Thus, ECT appeared to be associated with at least a 5-fold reduction in the likelihood of suicide during 2 years of follow-up. On the other hand, in a large scale epidemiological investigation, Babigian and Guttmacher (1984) found no advantage of ECT in preventing the occurrence of suicide within 5 years of first hospitalisation for depression. This study was conducted during a period when antidepressant drugs had become generally available (1961 to 1975), and lack of information on the treatment received by these patients during the intervening 5 years makes this study difficult to interpret (Tanney 1986). Overall, it appears that ECT is probably far more effective than no treatment in reducing the risk of suicide in patients with severe affective illness. Avery and Winokur's (1978) findings suggest that ECT may be more effective than first-generation antidepressants, which may be no more effective than no treatment.

2.2 Mianserin, Maprotiline and Amitriptyline

One of the first studies to examine the possibility that antidepressants may differ in their capacity to ameliorate suicidal ideation was conducted by Montgomery et al. (1978). They studied 80 patients with primary depression who were enrolled in 1 of 2 comparable double-blind treatment protocols. Altogether, 50 patients received mianserin (60mg daily), 15 received maprotiline (150mg in the evening), and 15 received amitriptyline (150mg in the evening). The 3 groups were equivalent in their pretreatment ratings. Mianserin produced a substantially greater degree of amelioration in suicidal ideation on the Montgomery & Åsberg Depression Rating Scale (MADRS) [1979] than maprotiline (11 *vs* 5.5; $p < 0.01$), and there was a trend in favour of mianserin over amitriptyline (11 *vs* 6; $p < 0.10$). The suicidal thought item on the Hamilton Depression Rating Scale (HAM-D) showed the same general tendency, though differences between drugs failed to attain statistical significance by this instrument. Mianserin also produced a significantly greater amelioration in pessimistic thoughts on the MADRS than maprotiline ($p < 0.02$), but there were no significant differences between mianserin and amitriptyline by this measure.

In short, though all 3 antidepressants appeared to exert roughly comparable effects on global depression ratings, their profiles differed in regard to specific depressive symptoms, and mianserin appeared to have a greater ameliorating effect on suicidal ideation and pessimistic thoughts than maprotiline. This study, however, did not explore

the possibility that drugs could enhance suicidal ideation.

2.3 Mianserin, Fluoxetine and Flupenthixol in Non-Depressed Patients with Recurrent Suicide Attempts

Montgomery et al. (1983) conducted a double-blind, placebo-controlled study of the efficacy of mianserin (30mg at night) in reducing suicidal behaviour in a group of 58 high-risk patients with multiple suicide attempts who suffered from personality disorders (borderline or histrionic). There were no differences in outcome between mianserin and placebo recipients at any time. More recently, Montgomery and colleagues (personal communication) have conducted a similar double-blind, placebo-controlled study of fluoxetine in this patient population. Again, they failed to find any indication of drug efficacy in reducing suicide attempts in non-depressed patients with personality disorders and parasuicidal behaviour. On the other hand, they found in a similar study (Montgomery et al. 1979) that the depot neuroleptic flupenthixol (20mg 4-weekly) reduced the suicide attempt rate to only 21% ($n = 14$) in this high-risk population over 6 months, which was far lower than injected placebo (75%, $n = 16$; $p < 0.05$).

2.4 Fluoxetine, Mianserin and Placebo

Muijen et al. (1988) conducted a double-blind, placebo-controlled study of fluoxetine and mianserin in the treatment of depression. 26 patients received fluoxetine, 27 received mianserin and 28 received placebo. Dose titration was rapid, with patients receiving 40 mg/day of fluoxetine or mianserin during week 1, 60 mg/day in week 2 and, if clinically indicated, 80 mg/day from week 3 onward. They emphasised in their report that fluoxetine produced a greater reduction in suicide ratings on the MADRS than placebo at week 7 ($p < 0.01$), and a greater reduction than mianserin at week 6 ($p < 0.01$). Not emphasised in the abstract or discussion section was the fact that 2 patients receiving fluoxetine (7.7%) made an overdose attempt within 2 weeks of starting the study, and that these patients had severely deteriorated, requiring hospitalisation and exclusion from the study. In contrast, only 1 mianserin recipient (3.7%) made an overdose attempt, and they allowed this patient to remain in the study, as his attempt was so minor. Furthermore, it appeared that no patients in the placebo group made an overdose attempt. Thus, it is hard to accept their conclusion that fluoxetine exerted a superior effect on suicidality. The exclusion of the 2 patients who made overdose attempts in the fluoxetine group, and the inclusion of the patient who made an overdose attempt in the mianserin group, almost certainly biased their statistical results.

2.5 Maprotiline and Placebo

Rouillon et al. (1989) reported the results of a year-long, double-blind, placebo-controlled study of the TCA maprotiline in outpatients. They found that there were 14 suicidal acts (9 attempts and 5 fatalities) out of 767 patients prescribed maprotiline, and only 1 suicidal act (fatality) among the 374 patients prescribed placebo ($p = 0.028$), suggesting that maprotiline augments suicidal tendencies. Nevertheless, maprotiline was clearly an effective antidepressant, and the majority of patients responded favourably. The fairly strong energising effect of maprotiline, coupled with its weak ameliorative effects on suicidal ideation and pessimism (Montgomery et al. 1978), may have been responsible for the numerically greater incidence of suicide attempts in patients receiving this drug.

2.6 *De Novo* Emergence of Suicidal Ideation During Treatment with Fluoxetine and Other Antidepressants

In an attempt to discover the incidence of emerging suicidal preoccupation during treatment with antidepressants, Fava and Rosenbaum (1991) surveyed 27 psychiatrists retrospectively. Data were collected on physicians' impressions of 1017 outpatients treated with antidepressants to ascertain the number of patients who first developed suici-

dal ideation or behaviour after the initiation of drug treatment. Clinical interviews were not conducted with these patients. However, the authors concluded that none of these patients developed suicidal thoughts of the degree and intensity reported by Teicher et al. (1990). Notwithstanding, they found that new suicidal ideation emerged in 3.5% (8 of 231) of patients treated with fluoxetine alone, and in 6.5% (4 of 62) of patients who received fluoxetine in combination with TCAs. Suicidal ideation emerged in 1.3% (5 of 385) of patients treated with TCAs alone or in combination with lithium, and in 3% (3 of 101) of patients treated with other non-TCAs (mostly trazodone). None of 63 of the patients treated with an MAOI were reported to have developed suicidal ideation after initiation of treatment. The authors concluded that the percentage of patients developing suicidal ideation, while higher for the fluoxetine recipients, did not significantly differ between any of these groups. However, while their sample size and statistical test had sufficient power to detect a difference between a 3.5% incidence in the fluoxetine group and a 0% incidence in the TCA group, they did not have a sufficient sample size to detect a difference between a 3.5% incidence for fluoxetine [estimated by Teicher et al. (1990)] and a 1% incidence for older antidepressants [as estimated by Damluji & Ferguson (1988)].

If we pool data to derive statistically-adequate samples a very different set of conclusions is reached. First, the incidence of emergent suicidal ideation in patients receiving fluoxetine treatment without or without TCAs (12 of 293, 4.1%) was significantly higher than those receiving treatment with any other agent (8 of 549, 1.5%; $p = 0.029$). Secondly, if patients in the 'other group' were excluded, as they largely received the selective serotonergic antidepressant trazodone, we find that patients receiving fluoxetine treatment were at least 3-fold more likely to develop new suicidal ideation than those treated with TCAs (with or without lithium) and MAOIs [4.1 *vs* 1.1% (5 of 448); $p = 0.011$ (*vs* fluoxetine with or without a TCA)]. Similarly, the *de novo* suicidal ideation rate was greater in patients receiving fluoxetine alone (3.5%, 8 of 231), than those receiving either TCAs (with or without lithium) or MAOIs ($p = 0.042$). In short, Fava and Rosenbaum's conclusions that there were no differences in the incidence of *de novo* suicidal ideation among these groups represents a classic beta error in which, because of inadequate sample size, they failed to detect true statistical differences.

2.7 Fluoxetine, TCAs and Placebo

Recently, Beasley et al. (1991) at the Lilly Research Laboratories conducted a retrospective reanalysis of their US Investigational New Drug (IND) application database that included all double-blind controlled clinical trials of fluoxetine for depression presented to the US Food and Drug Administration (FDA) for marketing approval for fluoxetine. Data were available on the incidence of known suicide attempts during the clinical trials (which almost invariably had a 6-week double-blind treatment phase), and they also had data on item 3 of the HAM-D, which provides some measure of suicidal ideation. Altogether, data were available on 3065 patients.

As indicated in table II, the aggregate incidence of suicide attempts during double-blind treatment was 3.40 per 1000 on fluoxetine, 1.76 per 1000 on placebo and 4.10 per 1000 on TCAs (imipramine or amitriptyline). Even with this rather large meta-analysis, this was an inadequate sample size to demonstrate statistical differences in the rate of occurrence of suicide attempts. Numerically, suicide attempts were at least as likely to occur during drug treatment as they were during placebo treatment.

Worsening of suicidal ideation (HAM-D item 3) occurred in 15.3% of patients receiving fluoxetine, 17.9% of placebo recipients and 16.3% of patients receiving TCAs. Overall, these rates were highly comparable. Substantial worsening of suicidal ideation (change in item 3 from 0 or 1, to 3 or 4) occurred in 1.17% of patients on fluoxetine, 2.63% of placebo recipients and 3.59% of patients on TCAs. Statistically, substantial worsening occurred marginally less often with fluoxetine than placebo ($p = 0.053$), or much less often on fluoxetine than on TCAs ($p = 0.004$).

Table II. Summary of Dista/Lilly and US FDA clinical trial data on fluoxetine, tricyclic antidepressants (TCAs) and placebo concerning suicidal ideation and overdose attempts

Treatment	Parameters	Overdose attempts	Worsening of suicidal ideation	Substantial worsening	Improvement in suicidal ideation
Placebo	Sample size	569	559	380	396
	Number (%)	1 (0.18)	100 (17.89)	10 (2.63)	217 (54.80)
Fluoxetine	Sample size	1765	1716	1201	1098
	Number (%)	6 (0.34)	262 (15.27)	14 (1.17)	793 (72.22)
TCAs	Sample size	731	720	418	559
	Number (%)	3 (0.41)	117 (16.25)	15 (3.59)	390 (69.77)
Statistical analyses (test)					
Fluoxetine + TCAs *vs* placebo (Pearson χ^2)		Sample size too small, given average incidence	$p = 0.332$	$p = 0.005$	$p < 0.0001$
Fluoxetine + TCAs *vs* placebo (Fisher Exact)			$p = 0.179$	$p = 0.302$	$p < 0.0001$
Fluoxetine *vs* placebo (Fisher Exact)			$p = 0.143$	$p = 0.053$	$p < 0.0001$
TCAs *vs* placebo (Fisher Exact)			$p = 0453$	$p = 0.543$	$p < 0.0001$
Fluoxetine *vs* TCAs (Fisher Exact)			$p = 0.541$	$p = 0.004$	$p = 0.301$

Improvement in suicidal ideation occurred in 72.2% of fluoxetine recipients and 69.8% of patients on TCAs, but such improvement occurred in only 54.8% of patients on placebo (fluoxetine *vs* placebo, $p < 0.001$; TCAs *vs* placebo, $p < 0.001$). Thus, active medication was more likely to reduce suicidal ideation in these studies than placebo.

The major weakness in this retrospective analysis is forced dependence on item 3 of the HAM-D as the sole measure of suicidal ideation. Although the authors state that this item 'systematically rates' suicidal ideation, this is hardly the case. First, the 21-item HAM-D is often administered in 20 minutes or less, providing little in-depth analysis of suicidal ideation in patients who are often reluctant to reveal their true feelings about suicide, particularly to an examiner with whom they may not have a therapeutic alliance. Secondly, as this item is embedded in a depression rating scale, it is susceptible to 'halo' effects (inaccurate biasing by alteration in overall depression score). Thirdly, the investigators misstate the manner in which this item is scored. They state that '0 = absence of such (suicidal) ideation; 1 = doubtful or trivial ideation; 2 = mild ideation; 3 = active suicidal ideation and suggestive behaviours; 4 = severe ideation usually involving a suicidal act' (Beasley et al. 1991). According to Hamilton (1967) the item is actually scored as follows: 0 = absent; 1 = feels life is not worth living; 2 = wishes he were dead or any thoughts of possible death to self; 3 = suicide ideas or gestures; 4 = attempts at suicide (only serious attempts rate 4). We had previously informed Lilly that item 3 of the HAM-D was too crude a metric to detect the obsessive suicidal preoccupation reported by Teicher et al. (1990), as patient 1 in this report was enrolled in one of the Lilly clinical trials. She had mild, passive, inconsequential, suicidal thoughts that scored a 3 on item 3 before fluoxetine treatment, and then developed an obsessive, unshakeable preoccupation with suicide during treatment, but did not make a serious suicide attempt, and thus still scored 3 on item 3.

Nevertheless, 2 basic ideas emerge from this retrospective reanalysis. First, fluoxetine and TCAs appear to diminish suicidal ideation in a significantly greater percentage of depressed patients than placebo. Secondly, fluoxetine and TCAs do *not* re-

duce the risk for suicide attempts. Given these 2 observations, we need to consider the possibility that fluoxetine and TCAs may redistribute suicide risk: reducing risk in a subgroup of responsive patients, while possibly augmenting risk in another less responsive subgroup. Indeed, if we assume that suicide attempts occurred in the population of patients whose suicidal ideation was not improved by treatment, then the 'suicidally unimproved' patients receiving active medication were numerically 3-fold more likely to attempt suicide than those receiving placebo [number of suicide attempts per patient whose suicidal thoughts were not improved: fluoxetine 6 of 305 (1.97%); TCAs 3 of 169 (1.78%); placebo 1 of 179 (0.56%)]. Simple inspection of overall risk rates would fail to detect the possibility that antidepressants may redistribute suicide risk: decreasing risk in certain patients, while enhancing risks in others, if the overall risk rate remains unchanged.

More recently, scientists at Dista/Lilly have published data on the relationship between fluoxetine and suicidal ideation and suicidal acts, based on reanalysis of double-blind trials of fluoxetine for bulimia nervosa (Wheadon et al. 1992), and OCD (Beasley et al. 1992). The results of these studies were similar to those for depression. In bulimia nervosa, data were presented for 554 patients treated with fluoxetine and 231 with placebo (Wheadon et al. 1992). Overall, fluoxetine diminished suicidal ideation more effectively than placebo in patients with significant initial suicidal ideation (77.7 *vs* 56.8% reduction, $p = 0.026$). Emergence of substantial suicidal ideation, or text-defined suicidal ideation, occurred statistically at the same rate in patients receiving fluoxetine or placebo. Fluoxetine failed to exert a protective effect against suicidal acts, which occurred in 7 patients receiving drug (1.3%), and in 2 patients receiving placebo (0.9%). If we assume that suicide attempts occurred in patients whose suicidal ideation was not improved by treatment, or had substantially worsened, then fluoxetine numerically increased the likelihood of a suicide attempt in this nonresponsive subsample [fluoxetine 7 of 96 (7.29%), placebo 2 of 70 (2.86%)].

In the OCD studies, data were available on 266 patients receiving fluoxetine and 89 patients receiving placebo (Beasley et al. 1992). No suicidal acts were committed by any patient. Fluoxetine produced a greater attenuation in HAM-D item 3 suicide ideation scores than placebo ($p = 0.003$). Twice as many patients receiving placebo (3.6%) experienced substantial worsening in their HAM-D item 3 suicidal ideation score than patients receiving fluoxetine (1.7%), though this difference was not statistically significant. On the other hand, clinical detection of suicidal ideation as a treatment emergent adverse event occurred in 3 patients, all of whom were receiving the highest dosage of fluoxetine (60 mg/day, $n = 90$), and in none of the patients receiving placebo. This observation underscores our concern that a change in item 3 of the HAM-D may not be a clinically meaningful gauge of worsening suicidal ideation.

Overall, these 3 major meta-analyses, though not prospectively designed to assess the effects of fluoxetine on suicidal ideation and self-destructive behaviour, provide some reassurance. They all clearly indicate that fluoxetine was more effective than placebo in attenuating suicidal ideation, and suggest that substantial worsening of suicidal ideation may occur no more frequently on fluoxetine than placebo. However, they also indicate that despite fluoxetine's superiority in attenuating suicidal ideation, this agent affords no protection against the occurrence of suicidal acts in patients with depression or bulimia nervosa. This suggests that the smaller percentage of patients on fluoxetine whose suicidal ideation has worsened or failed to improve may be more prone to act.

2.8 Suicidal Behaviour On and Off Lithium

Although our literature review has shown that antidepressants, on average, fail to provide much protection against attempted or completed suicide, it appears that lithium prophylaxis may exert a strong protective effect in bipolar (manic-depressive) patients. Recently, Müller-Oerlinghausen et al. (1992) provided some strong preliminary data on this possibility. They studied 68 patients in a

lithium clinic over a mean observation period of 8 years. Each patient had made at least 1 suicide attempt prior to lithium treatment, and had received at least 12 months' lithium treatment prior to inclusion. Only 1 of 54 patients (1.8%) committed suicide who had remained stable on lithium, and who had a significant lithium concentration at the time of his previous appointment. Conversely, there were 4 suicides during this period out of 13 patients (30.8%) who had discontinued lithium ($p < 0.01$). Moreover, only 4 patients on continuous lithium treatment attempted suicide (7.4%) compared with 53.8% of those who discontinued it ($p < 0.001$).

In short, 84.6% of bipolar patients discontinuing lithium either killed themselves or made a serious suicide attempt. During the time they were taking lithium, only 6% of the patients in the group had made a suicide attempt. The authors further emphasise that 3 suicide or parasuicidal outcomes in this group were directly related to a decision on the part of the treating physician to discontinue lithium, rather than the patients' wish to stop medication.

Finally, lithium appeared to provide the same degree of protection against suicidal acts in responsive patients as it did in nonresponders. Hence, the authors argue that lithium can exert a protective antiaggressive effect, even when it fails to adequately stabilise mood. This is potentially a very important observation that warrants considerable attention.

2.9 Antidepressants and the Frequency of Fatal Overdoses

Fatal poisonings in Great Britain are reported at coroners' inquests and are published annually. This database has allowed investigators to estimate fatal toxicity indices for different antidepressants based on cases of single drug fatalities. Assumptions have been made to derive data on the number of patients who have received these medications (Montgomery & Pinder 1987), or on the number of prescriptions written for their use (Cassidy & Henry 1987; Farmer & Pinder 1989; Henry 1989), though these assumptions appear reasonable. It is noteworthy that there is a marked difference between these medications in the number of fatal overdoses per million prescriptions. For drugs in which there were at least 10 fatal overdoses reported in the period 1975 to 1984 (Cassidy & Henry 1987) or 1975 to 1985 (Montgomery et al. 1989), the number of deaths per million prescriptions ranged from 80.2 for desipramine to 6.2 for mianserin. Thus, the frequency with which patients fatally overdose on different antidepressants may vary by as much as 15-fold.

Montgomery et al. (1989) discussed a number of factors that may account for the higher rate of fatal overdoses with certain antidepressants. These factors include differences in the inherent toxicity of these drugs, differences in the patient populations to whom they are prescribed and differences in the manner in which they may be prescribed (e.g. certain antidepressants may be prescribed more frequently in subtherapeutic doses). Prescribers should be aware of this, as it suggests that antidepressant drugs vary in their safety margin and that all things being equal, it may be prudent to prescribe antidepressants with lower fatal toxicity indices.

2.10 Estimated Overdose Proclivity Rate for Antidepressants

We have assumed that the fatal toxicity index (number of deaths per million prescriptions) presented by Cassidy and Henry (1987) and Montgomery et al. (1989) is mathematically proportional to 2 factors: the number of overdose attempts made on each drug, and the inherent toxicity of the medication. It would certainly be expected that a greater proportion of overdose attempts would prove fatal with a highly toxic drug than with a less toxic agent. Thus, we reasoned that if the fatal toxicity index data were corrected for differences in the toxicity of each agent, we might derive an estimate of overdose proclivity for these drugs based on this extremely large epidemiological sample. To estimate the toxicity of the more commonly prescribed antidepressants, we calculated a composite

therapeutic index based on the ratio of the oral toxicity [lethal dose in 50% (LD_{50})] in rats to the maximum prescribed dosage in Great Britain (Cassidy & Henry 1987), expressed in mg/kg for an average 75kg adult. LD_{50} data were obtained from a number of sources (Merck Index 1989; Physicians' Desk Reference 1991; Usdin & Efron 1972), and individual pharmaceutical manufacturers when necessary. Data were averaged to provide the most meaningful and consistent LD_{50} estimate. For 1 drug, tranylcypromine, data could only be found for the LD_{50} in mice. We then multiplied the fatal toxicity index by the composite therapeutic index to obtain the estimated overdose proclivity rate (table III).

Although this mathematical conversion is quite tentative, 3 pieces of evidence suggest that it may have meaning. First, actual clinical overdose attempt rates are known for 3 antidepressants on the basis of large samples receiving treatment for meaningful clinical periods. Inman (1988) reported that 92 patients out of 26 781 receiving treatment with mianserin in general clinical practice made an overdose attempt involving mianserin (3.44 per 1000), whereas 246 patients out of 42 082 treated with amitriptyline made an overdose attempt involving amitriptyline (5.85 per 1000). We also know from the Rouillon et al. study (1989) that 9 of 767 patients (11.73 per 1000) receiving year-long treatment with maprotiline made a suicide attempt. Our estimated overdose proclivity rate provides the correct rank ordering, which the fatal toxicity datum does not. The estimated overdose risk also provides an exact linear correlation with the known overdose risk data ($r = 1.0$).

Secondly, the 3 commonly prescribed MAOIs tranylcypromine, phenelzine and isocarboxazid differ substantially in their fatal toxicity index (58.1, 27.8 and 12.8, respectively), but have very similar estimated overdose proclivity rates (5.5, 6.0 and 4.5, respectively) after adjustment for differences in toxicity. Similarly, the group of selective noradrenergic uptake inhibitor antidepressants with relatively low anticholinergic adverse effects – desipramine, nortriptyline and maprotiline – have very different fatal toxicity indices (80.2, 40.8 and 35.7, respectively), but have very similar estimated overdose proclivity rates (16.4, 15.4 and 15.4, respectively) after correction for toxicity. This suggests that toxicological correction yields comparable estimated overdose proclivity rates across agents with similar pharmacological and clinical profiles.

Thirdly, the TCAs clomipramine and protriptyline have very low fatal toxicity indices compared with other TCAs. It has been argued that the lower incidence of fatal overdoses with clomipramine is due to its use in OCD, as this population is less suicidal than depressed patients. However, clomipramine is also used extensively in severely depressed, treatment-resistant patients, who would be expected to be at greater risk for suicide (Montgomery et al. 1989). Nevertheless, using this correction factor, clomipramine and protriptyline have estimated overdose proclivity rates that are comparable with other TCAs.

If this analytical approach has any validity, it suggests that members of the same pharmacological class share similar risk for overdose attempts. It also suggests that the highly selective noradrenergic reuptake inhibitors desipramine, nortriptyline and maprotiline may be associated with a greater risk for overdose attempt than other pharmacological classes. This is clearly consonant with the Feuerstein and Jackisch (1980) hypothesis. Unfortunately, comparative data on the selective serotonin uptake inhibitors are not yet available. The data also emphasise that antidepressants may differ in the degree to which they enhance or antagonise suicidal impulses. We cannot tell whether these hypothesised differences are a consequence of the drug's pharmacological profile, or whether they are due to differential prescribing practices (e.g. preferential use of selective noradrenaline uptake inhibitors in patients with greater inherent likelihood to make overdose attempts). However, we do know that antidepressants often assumed to be safer in overdose attempts, that are often prescribed to patients at risk for suicide (e.g. trazodone, mianserin), have low estimated overdose proclivity rates, suggesting that this is not a major determinant. These findings suggest that additional research

Table III. Number of fatal overdoses, toxicity and estimated overdose proclivity rates for antidepressants commonly prescribed in the UK

Antidepressant	Year introduced	No. of fatal poisonings (1975-1985)	Deaths per million scripts (1975-85)	Estimated no. of scripts (millions)	Maximum UK dose[a] (mg/kg)	Mean rat oral LD_{50} (mg)	Therapeutic index (estimated) [LD_{50}/ maximum dose]	Overdose proclivity rate (estimate)	Known overdose risk rate (per 1000)
Monoamine uptake inhibitors									
Noradrenaline (norepinephrine) >> serotonin									
Desipramine[b]	1963	13	80.2	0.162	2.67	544.0	204.0	16.4	
Maprotiline[c]	1974	33	35.7	0.924	2.00	865.0	432.5	15.4	11.73
Nortriptyline[c]	1963	62	40.8	1.520	1.33	503.0	377.3	15.4	
Protriptyline[c]	1966	6	10.1	0.594	0.80	450.0	562.5	5.7	
Weighted average								13.7	
Noradrenaline > serotonin									
Amitriptyline[c]	1961	1282	46.9	27.335	2.67	422.0	158.3	7.4	5.85
Dothiepin[c]	1969	603	48.6	12.407	3.00	450.0	150.0	7.3	
Doxepin[c]	1969	110	30.8	3.571	4.00	277.5	69.4	2.1	
Imipramine[c]	1959	299	28.5	10.491	3.00	496.0	165.3	4.7	
Weighted average								6.5	
Serotonin > noradrenaline									
Clomipramine[c]	1970	55	10.6	5.189	2.00	1450.0	725.0	7.7	
Atypicals (weak uptake inhibitors)									
Butriptyline[b]	1975	1	7.5	0.133	2.00	345.0	172.5	1.3	
Iprindole[b]	1967	2	7.8	0.256	1.60	775.0	484.4	3.8	
Mianserin[c]	1976	41	6.2	6.613	1.20	842.5	702.1	4.4	3.44
Trazodone[c]	1980	6	11	0.545	4.00	486.0	121.5	1.3	
Trimipramine[c]	1966	169	27.9	6.057	4.00	800.0	200.0	5.8	
Weighted average								4.7	
Monoamine oxidase inhibitors									
Tranylcypromine[b]	1960	15	58.1	0.258	0.40	38.0	95.0	5.5	
Phenelzine[b]	1959	24	22.8	1.053	0.80	210.0	262.5	6.0	
Isocarboxazid[b]	1960	3	12.8	0.234	0.80	280.0	350.0	4.5	
Weighted average								5.7	

a 75kg man.
b Cassidy & Henry (1987).
c Montgomery et al. (1989).
Abbreviations: LD_{50} = lethal dose in 50% of animals.

needs to be conducted on the differential effects of antidepressants on suicidal thoughts and actions.

3. *Conclusions*

Although antidepressant drugs are of undeniable value and are the cornerstone of treatment of patients with moderate to severe depression, they are neither universally efficacious nor free from serious risk. Although these agents often diminish suicidal ideation in depressed patients, they do not do so in all patients, and some patients receiving these medications experience worsening or *de novo* emergence of suicidal ideation during treatment (e.g. Beasley et al. 1991; Fava & Rosenbaum 1991). It also appears that some antidepressant drugs have little propensity to attenuate suicidal ideation in patients with personality disorders (Montgomery et al. 1983), and other antidepressants may exacerbate risk (Soloff et al. 1986). Available data suggest that the risk for overdose attempt on antidepressants may be no better on active medication than placebo (Beasley et al. 1991, 1992), and for maprotiline it may be worse (Rouillon et al. 1989). Studies also suggest that antidepressants differ in their capacity to reduce suicidal ideation (Montgomery et al. 1978), and they clearly differ in their association with fatal overdoses. From large sample studies, it also appears that these agents may differ in the frequency with which patients prescribed these medications make overdose or suicide attempts (Inman 1988). Although clinically effective antidepressant drugs have been available for more than 30 years, the relationship between these medications and suicide has received relatively little attention, and most of this interest has occurred in the last few years. We are particularly concerned with the possibility that antidepressant drugs may redistribute suicidal risk, diminishing it in some patients who respond very favourably to the medication, while possibly enhancing it in other patients who respond more poorly. Very sophisticated studies will need to be conducted to ascertain whether this is true if, on balance, the antidepressant produces an overall incidence rate similar to placebo.

Some clinicians categorically reject the possibility that antidepressants can induce or enhance suicidal tendencies. We provide 9 clinically plausible mechanisms through which this may occur. Other clinicians suggest that all cases of suicidal ideation emerging on antidepressants must be due to the patient's underlying depression, as suicidal ideation is a symptom of depression. This argument is puzzling since clinicians have no difficulty accepting that antidepressant drugs can exacerbate or induce insomnia, anorexia, agitation, anxiety and loss of libido in depressed patients, though these are also frequent symptoms of depression. Suicidal ideation may represent a special exception to this logic, but we have found no evidence to suggest that it does. We should clarify that we are not proposing that the medication plants a specific series of thoughts in people's minds. Rather, we are suggesting that, in some instances, the medication may interfere with normal neuropsychological processes that keep suicidal thoughts from intruding into consciousness, or which normally enable patients to reject these thoughts once they emerge.

We should also emphasise that antidepressant agents are not the only drugs that may induce or enhance suicidal tendencies. It is believed that certain antihypertensive medications are associated with the emergence of depression, and may lead, in rare instances, to suicide. Perhaps the most worrying finding was reported by Brent et al. (1987). They examined 15 children with epilepsy treated with phenobarbital and 24 with carbamazepine. The groups were similar across a wide range of demographic, seizure-related, familial and environmental factors. Patients treated with phenobarbital had a much higher prevalence of major depression (40 *vs* 4%, $p = 0.02$), and a much greater prevalence of suicidal ideation (47 *vs* 4%, $p = 0.005$), suggesting that in this patient population phenobarbital may induce both depression and suicidal ideation. Benzodiazepines have also been associated with the emergence of suicidal ideation in case reports (Hall & Joffe 1972; Ryan et al. 1968; Styron 1990). We believe that it is time to recognise that suicide is not merely a metaphysical construct, but a mental or behavioural state with firm roots in

our neurochemistry, which may be affected, for better or worse, by pharmacological agents.

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