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New classes of antidepressant drugs

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The January 1997 issue of this journal contained four reviews that compared tricyclic antidepressants with selective serotonin reuptake inhibitors (SSRIs) and other newer antidepressants in terms of their pharmacology (Palazidou, 1997), adverse effects, potential drug interactions and toxicity (Henry, 1997), efficacy in the prevention of relapse and recurrence (Edwards, 1997), and findings from meta-analyses (Anderson, 1997). In July 1997 reboxetine was promoted as the first selective noradrenaline reuptake inhibitor (NARI), and in October of the same year mirtazapine was promoted as the first noradrenergic and specific serotonergic antidepressant (NaSSA). Milnacipran is presently being registered by the manufacturers, after which it will be the second antidepressant drug promoted as a specific serotonin and noradrenaline reuptake inhibitor (SNRI).

Unresolved controversies about newer antidepressants

Box 1 lists some of the unresolved controversies about newer antidepressant drugs. Most of these questions were prompted by the increasing popularity of SSRIs in general practice and in psychiatric practice. It seems inevitable that most of these questions will also be asked of the latest antidepressant drugs.

SNRIs

There has been major research investment in the search for compounds that have the antidepressant effect of tricyclic antidepressant drugs, but without the significant interactions at receptors associated with their typical adverse effects. SNRIs like venlafaxine and milnacipran inhibit selectively the

Box 1. Unresolved controversies about the merits of newer antidepressant drugs

Posology – do SSRIs in clinical practice have substantial advantages because they can be taken only once a day and the initial dose may be therapeutic?

Efficacy – are newer antidepressants (particularly citalopram, paroxetine, trazodone and moclobemide) as effective in severe depression as tricyclic drugs?

Adverse effects – are the costs of newer antidepressants justified by the modest reductions in drop-out because of adverse effects?

Adherence – is adherence to antidepressant drug treatment simply determined by the number and severity of adverse effects?

Toxicity – will the increased prescription of newer antidepressants lead to any reduction in suicide? (Most patients with depression who kill themselves do not do so with prescribed antidepressant drugs.)

Continuation treatment – will better tolerability enhance treatment adherence?

Cost – could the money spent on newer antidepressants be better invested elsewhere in mental health services?

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reuptake of both serotonin and noradrenaline without any significant affinity for adrenergic, muscarinic or histaminergic receptors. Consequently, these compounds are not associated with the orthostatic hypotension, anticholinergic effects (dry mouth, constipation, blurred vision) and sedation seen commonly with tricyclic antidepressants. The clinical pharmacology of these drugs has been reviewed by Briley (1998) and Burnett & Dinan (1998).

Venlafaxine

Venlafaxine is a bicyclic compound with a chemical structure unrelated to existing antidepressant drugs. Laboratory experiments in rat brains have shown that venlafaxine is five times more potent in its inhibition of the reuptake of serotonin than noradrenaline. It is distinct from milnacipran in that it also weakly inhibits the reuptake of dopamine. It undergoes an extensive first-pass metabolism in the liver to give *O*-demethylvenlafaxine, which has similar pharmacological properties and also preferentially inhibits the reuptake of serotonin. Venlafaxine can reduce the functional activity of β-adrenergic receptors in rat brain after a single administration. This is an unusual effect for an antidepressant drug and led to the suggestion that venlafaxine might have a rapid onset of antidepressant effect.

Venlafaxine is well absorbed after oral intake and has a half-life of approximately four hours, although *O*-demethylvenlafaxine has a half-life approximately twice as long. The relatively short half-life means that a steady state is reached within a few days, but has the disadvantage that more than once daily dosing is required. Initial clinical studies evaluated doses given three times a day, although later studies used twice daily dosing. An extended-release preparation of venlafaxine has been made available that need be taken only once a day.

There have been several large-scale studies that have included a comparison of the antidepressant effect of venlafaxine with that of placebo treatment, mostly involving out-patients with depression in the USA. In some cases the full details of these studies are held as data on file with the manufacturer, but fuller details are now being published (Rudolph *et al*, 1998). The findings were that venlafaxine had to be taken at a dose of at least 75 mg per day to have a significantly greater antidepressant effect than placebo tablets, and that there was a significant dose–response relationship with venlafaxine, that is, the percentage of patients meeting a pre-determined definition of clinical response rose as the daily dose of venlafaxine increased from 75 to 150–225 mg and to 300–375 mg per day. One of the placebo-controlled studies that confirmed the antidepressant effect of venlafaxine was conducted among 93 in-patients who suffered from major depression of melancholic subtype (Guelfi *et al*, 1995). Depression rating scores were significantly lower among the patients treated by venlafaxine than among those treated by placebo after one week, but it must be noted that patients were prescribed a dose of 300 mg per day by this time.

Venlafaxine was at least as effective as imipramine in a study of 167 in-patients suffering from major depression of melancholic subtype (Benkert *et al*, 1996). There was some evidence of a more rapid onset of antidepressant effect with venlafaxine, but it should be noted that venlafaxine was given at its full dose over the first five days whereas the maximum permissible dose of imipramine was 200 mg daily throughout. The comparison with clomipramine may be of particular interest because it is a potent inhibitor of the reuptake of both serotonin and noradrenaline and is, therefore, held by some psychiatrists to be the drug of choice for severe depressive illness. Unfortunately, the average treatment dose was only 105 mg per day for either drug and the study's relevance to psychiatric practice was uncertain (Samuelian *et al*, 1992). The comparisons with fluoxetine are also of interest because it is the best-selling branded antidepressant drug in the world, and because of the theoretical question of whether an antidepressant that inhibits both the reuptake of serotonin and noradrenaline is more effective than an antidepressant drug that inhibits the reuptake of serotonin alone. No difference was found in a large 12-week study conducted in general practice settings in the UK that compared venlafaxine 37.5 mg twice per day with fluoxetine 20 mg once daily (Tylee *et al*, 1997). Venlafaxine was more effective than fluoxetine in a large-scale study among depressed out-patients, but interpretation of this finding was complicated by the study design (Dierick *et al*, 1996). Patients allocated to treatment with fluoxetine were prescribed a fixed dose of 20 mg daily throughout the study, whereas it was permissible to vary the dose of venlafaxine from 75 to 150 mg daily depending on clinical improvement. A multi-centre comparison using fixed doses among 68 in-patients with depression of melancholic subtype found a significantly greater antidepressant effect after four and six weeks in patients randomly allocated to venlafaxine 200 mg daily than in patients allocated to fluoxetine 40 mg daily (Clerc *et al*, 1994).

The most common adverse effect is nausea. This affects about one-third of patients taking a daily dose of 75 mg and its prevalence increases with higher

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initial doses. The prevalence of nausea falls steeply after the first week of treatment, and continues to decline over six weeks of treatment. Among the more frequent adverse effects, somnolence, dry mouth, and sweating are dose-related. Sexual dysfunction is also dose-related. Insomnia, constipation and dizziness are not clearly dose-related. Elevated diastolic blood pressure was observed in approximately 5% of patients prescribed more than 200 mg daily and the monitoring of blood pressure is, therefore, recommended in such cases. The average probability of discontinuation because of adverse effects in treatment of the acute episode was broadly similar to that seen with the antidepressants against which venlafaxine had been compared, including tricyclic antidepressants. The probability of discontinuation because of adverse effects increases with higher prescribed doses of venlafaxine, presumably because several of the most frequent adverse effects are dose-related. One study found that discontinuation because of adverse effects during continuation treatment of up to one year was much less likely than with imipramine, but discontinuations for all reasons were substantial in both treatment groups.

Venlafaxine is not a significant inhibitor of the cytochrome pigment (CYP) 450 isoenzyme system, and it is therefore unlikely that the drug would inhibit the clearance of a drug metabolised by these pathways. Venlafaxine is itself metabolised by the CYP450 2D6 isoenzyme and caution has been recommended when it is administered with a potential inhibitor of the system, for example, cimetidine. As with other inhibitors of serotonin reuptake, there is the potential for a toxic interaction when the drug is given with a monoamine oxidase inhibitor (MAOI). Dose reductions are advised for patients with moderate renal or hepatic impairment. No specific dosage recommendations have been made for elderly patients. There is accumulating experience of intentional overdoses of venlafaxine, including one case where a patient made a full recovery after an ingested dose 90 times that of the usual daily dose. Somnolence is the most common feature and sinus tachycardia, prolongation of the Q–T interval and seizures have also been reported.

Discontinuation symptoms can occur with all antidepressant drugs, and severe discontinuation syndromes have been reported when venlafaxine is stopped abruptly. A gradual reduction over at least one week is recommended for all patients who have taken any dose of venlafaxine for six weeks or a high dose for any period of time.

The cost of initial doses of venlafaxine is presently similar to the initial doses of other newer antidepressant drugs, but recent studies in psychiatric practices have used high doses that are substantially more expensive.

Milnacipran

Milnacipran has a chemical structure unrelated to available antidepressant drugs. Unlike venlafaxine it inhibits the reuptake of noradrenaline and serotonin equally and does not inhibit the reuptake of dopamine. Unlike most antidepressant drugs, repeated administration of milnacipran has no functional effects on β-adrenergic receptors. Evidence that milnacipran has a significant antidepressant effect would not support the hypothesis that down-regulation of β-adrenergic receptor function was a characteristic biological effect of antidepressant drugs.

Milnacipran is rapidly absorbed after oral administration and its elimination half-life of approximately eight hours means it needs to be administered twice daily. It is mostly eliminated as the parent compound by the kidney and has no active metabolites.

There have been three comparisons of the antidepressant effect of milnacipran with that of placebo treatment in psychiatric practice (Puech *et al*, 1997). It was found that a dose of 50 mg twice per day was required to be more effective than placebo, but that a higher dose was not more effective. Several European studies have compared the antidepressant effect of milnacipran with existing antidepressants in psychiatric practice, but in most cases findings are available only in summary (Peuch *et al*, 1997). A meta-analysis of six comparisons of milnacipran given at a dose of 50 mg twice a day and imipramine given at a dose of either 50 or 75 mg twice a day in 662 patients with depression found no significant difference between the improvements in depression rating scores. Two comparisons of milnacipran with clomipramine at a dose of 150 mg daily in patients suffering major depression and who originally required hospital admission have found the fall in depression rating scores over 12 weeks to be greater for patients treated with clomipramine, although this difference was statistically significant in only one study. A comparison of milnacipran with fluoxetine at a dose of 20 mg a day in the treatment of endogenous depressive illness has been reported as a summary; the reductions in depression rating scores after 12 weeks were greater in patients prescribed milnacipran, but these differences were not statistically significant.

Vertigo was the most common adverse effect and affected 5% of patients. Sweating, anxiety, hot flushes and dysuria also occurred more commonly than with placebo treatment. Increased noradrenergic tone in the absence of any adrenoceptor blockade is believed to be responsible for the dysuria that occurs in approximately 2% of patients.

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Milnacipran is contraindicated among men with bladder outlet obstruction. The average probability of discontinuation because of adverse effects in treatment of the acute episode was 7.6%, half the probability found with comparator tricyclic antidepressant drugs and comparable to that found with comparator SSRIs.

Most of the drug is eliminated unchanged by the kidney, and a dosage reduction is recommended in renal impairment. It has no significant interactions with CYP isoenzymes and has no active metabolites. No dosage reduction is advised for the elderly or in hepatic impairment. The concomitant prescription of MAOIs is contraindicated.

There is increasing experience of intentional overdoses, including one case where a patient made a full recovery after a reported dose of six weeks' supply. Nausea or vomiting are the most common features and sinus tachycardia, sweating and respiratory difficulties have also been reported.

It is not yet known how much milnacipran will cost.

NARIs

Recent commercial interest in SSRIs has probably overshadowed the acknowledged importance of noradrenaline in the pathophysiology and treatment of depressive illness (Redmond & Leonard, 1997) and the attempts over many years to design drugs that specifically inhibited the reuptake of noradrenaline.

Reboxetine

The chemical structure of reboxetine has important similarities with viloxazine and, perhaps surprisingly, fluoxetine. It is a potent selective inhibitor of the reuptake of noradrenaline, and has little or no significant affinity for adrenergic receptors, muscarinic cholinergic receptors or histaminergic receptors.

Reboxetine is rapidly absorbed after oral administration and has an elimination half-life of approximately 12 hours. Twice daily dosing is required. About 10% of the drug is eliminated unchanged by the kidney and the rest is metabolised by several different pathways in the liver, although these have not been well described.

Most of the findings from investigations of the antidepressant effect of reboxetine have been made available only in summary form (Montgomery, 1997). There have been several comparisons of the antidepressant effect of reboxetine at a dose of 8–10 mg per day with placebo treatment of major depression in psychiatric practice; a significantly greater fall in depression rating scores was seen with reboxetine after 10 days. At the time of writing there have been no published comparisons of reboxetine with placebo treatment in elderly people. A published comparison of reboxetine at a dose of 4–5 mg twice a day and imipramine at a dose of 150–200 mg per day in the treatment of major depression in psychiatric practice found no significant difference in the reductions in depression rating scores over six weeks in a sample of 256 patients; the proportion of patients who achieved a predetermined definition of clinical response was significantly higher with reboxetine than imipramine (Berzewski *et al*, 1997). Two studies have included a comparison of reboxetine at a dose of 4–5 mg twice a day and fluoxetine at a dose of 20–40 mg daily among a total of 421 out-patients with depression. The proportions of patients who achieved clinical response were exactly the same in one study and not significantly different in the other study. Most patients in one study completed a self-rating questionnaire about social functioning that included items on work, spare-time activity, family relationships and ability to cope with resources and finances. Total scores were significantly better among the patients treated with reboxetine between six and eight weeks of treatment (Dubini *et al*, 1997). The promotion of reboxetine may lead to renewed interest in comparisons that have been undertaken between antidepressant drugs selective for the reuptake of noradrenaline and those selective for the reuptake of serotonin. Robertson *et al* (1994) compared fluoxetine, an SSRI, and lofepramine, a potent inhibitor of the reuptake of noradrenaline, in the treatment of 183 out-patients with depression and found no suggestion of any difference in antidepressant effect.

The most common adverse effect is a dry mouth, which affects approximately 25% of patients. Constipation, insomnia, increased sweating, tachycardia and vertigo also occur more commonly than with placebo treatment. Urinary hesitancy or impotence can affect 5% of patients. Dizziness or hypotension is uncommon but can lead to discontinuation. The average probability of discontinuation because of adverse effects in acute treatment studies was 10% for reboxetine compared to 14% for imipramine and 7% for fluoxetine (Mucci, 1997). The metabolism of reboxetine has not been fully characterised; consequently, azole antifungal agents, macrolide antibiotics and fluvoxamine are contraindicated. Caution has also been advised with anti-arrhythmic drugs, antipsychotic drugs and tricyclic antidepressants. The concomitant prescription of MAOIs is also contraindicated as a

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precautionary measure. An initial dose of only 2 mg twice a day is recommended in elderly patients and in patients with renal and hepatic impairment. Cases of intentional overdose with reboxetine known to the manufacturers included one patient who reportedly ingested one month's supply of the drug and fully recovered.

The cost of reboxetine is comparable to the initial doses of newer antidepressants.

NaSSAs

The discovery of the antidepressant effects of mianserin aroused considerable interest at the time because it had no significant effects on the reuptake of either serotonin or noradrenaline; it was, however, an α_2-adrenergic receptor antagonist and this stimulated investigation of these antagonists as putative antidepressants.

Mirtazapine

Mirtazapine has a tetracyclic chemical structure and has been shown in laboratory experiments in living rats to increase the rate of firing and neurotransmitter release in both noradrenaline-containing neurons in the hippocampus and serotonin-containing neurons in the dorsal raphe nucleus. The effect on serotonin-containing neurones is explained by the direct stimulation of released noradrenaline on α_1-adrenergic receptors sited on the cell bodies of serotonin-containing neurons and by mirtazapine's antagonism of inhibitory α_2-adrenergic receptors on serotonin-containing nerve terminals. This mode of action is unique (de Boer, 1996). Mirtazapine also blocks several subtypes of post-synaptic serotonin receptors including 5-HT_2 and 5-HT_3 receptors. Stimulation of these post-synaptic receptors resulting from treatment with tricyclic antidepressants and SSRIs has been suggested as the cause of the adverse effects of agitation, insomnia, sexual dysfunction and nausea.

Mirtazapine is rapidly absorbed after oral administration and has a half-life of elimination of at least 20 hours that allows once daily dosing. A steady state is achieved within four days. It is extensively metabolised through a number of pathways that are not dependent on a single hepatic isoenzyme. There is one active metabolite, demethylmirtazapine, but its pharmacological activity is one-tenth that of the parent compound.

Six flexible dosing studies have included a comparison of the antidepressant effect of mirtazapine (5–60 mg per day) with placebo in psychiatric practice. A published meta-analysis found that the antidepressant effect of mirtazapine was significantly greater than that of placebo after one week of treatment (Kasper, 1995). The relationship of clinical response to prescribed dose is held by the manufacturer as data on file. The minimum dose that will produce an antidepressant effect greater than placebo treatment has not been established. The starting dose recommended by the manufacturer is 30 mg daily because the prevalence of adverse effects attributable to mirtazapine's affinity for histamine receptors (somnolence and increased appetite) is less with this dose than with lower doses. Five flexible dosing trials compared the antidepressant effect of mirtazapine with amitriptyline in psychiatric practice, and this included one in 251 patients suffering endogenous depression and requiring hospital admission (Zivkov & de Jongh, 1995). A meta-analysis concluded that there was no significant difference in the reductions in depression rating scores over six weeks (Zivkov *et al*, 1995). The same result occurred in a multi-centre comparison of mirtazapine (20–80 mg per day) with clomipramine (50–200 mg per day) in 173 patients with moderate or severe depression who required hospital admission (Richou *et al*, 1995). The average dose of clomipramine in the last three weeks of treatment was 121 mg per day. The comparison with fluoxetine was conducted among 133 out-patients and in-patients, approximately 70% of whom suffered from major depression of melancholic subtype. Mirtazapine at a dose of 15–60 mg a day led to a significantly greater reduction in depression rating scores after three and four weeks than that seen with fluoxetine (20–40 mg per day), although the difference was not statistically significant at six weeks (Wheatley *et al*, 1998).

The most common adverse effect was a dry mouth, which affected approximately one-third of treated patients. The only other adverse effects that occurred more commonly than in patients taking placebo tablets were drowsiness, increased appetite and weight gain. There was no evidence that agitation, insomnia, sexual dysfunction or nausea occurred more commonly than in patients taking placebo tablets, which confirmed the therapeutic relevance of mirtazapine's blockade of 5-HT_2 and 5-HT_3 post-synaptic receptors. Reversible white blood cell disorders including agranulocytosis are mentioned as a special precaution, presumably because of mirtazapine's chemical similarity to mianserin. Post-marketing surveillance by the manufacturer involving approximately one million treatment courses with mirtazapine has not detected any evidence that the probability of agranulocytosis is above that expected among patients taking other antidepressant drugs. The probability of

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discontinuation because of adverse effects was on average 5% in comparison to approximately 9% in amitriptyline-treated patients in comparative studies. In the one direct comparison of mirtazapine and fluoxetine, the probabilities were 10.6 and 13.4%, respectively. Caution with dose escalation is recommended in patients with either hepatic or renal impairment, but no dosage reduction is recommended for elderly patients. Mirtazapine may potentiate the sedative effects of benzodiazepines or alcohol. The concomitant prescription of MAOIs is contraindicated. There is accumulating clinical experience of the safety of mirtazapine in intentional overdose, including one patient who reportedly ingested one month's supply of drug and recovered fully. Sedation has been reported, particularly in association with other psychotropic drugs, but no significant effects on cardiac function.

The cost of mirtazapine is comparable to the initial doses of other newer antidepressants.

Overview

SNRIs and NARIs are considered novel not because of their mode of action, but because they are selective in their inhibition of neurotransmitter reuptake and have few, if any, significant affinities for other neuroreceptors in the brain. Mirtazapine is the first available NaSSA and is different because its postulated mode of action is unique, and does not involve the classical mechanisms of reuptake inhibition or the inhibition of monoamine oxidase. This alone ought to remind us that the mode of action of antidepressant drugs is substantially more complicated than most accounts in psychiatric textbooks suggest (see Frazer, 1997). Box 2 lists some controversies that may be aroused by the introduction of these drugs.

It would be premature to draw conclusions about the superiority of one drug over another or one class of drug over another based on the evidence of only one or two acute treatment studies. Many of the available studies can be criticised because of what have become known as dosing inefficiencies, where the comparator antidepressant may not have been used at its optimal therapeutic dose, biasing the study in favour of the newer antidepressant. The tolerability of these latest antidepressants may not be equivalent, although the available evidence suggests they are less toxic in overdose than traditional tricyclic antidepressant drugs. Post-marketing surveillance and further research may yield important information about rare but potentially serious adverse effects, drug interactions and augmentation strategies. The reader is strongly advised to consult the latest product monograph or summary of product characteristics prepared by the manufacturers.

Box 2. Potential controversies prompted by new classes of antidepressant drugs.

Regulation of mood – **Has the marketing of SSRIs overshadowed the acknowledged role of other neurotransmitters?**

Mode of action – **Do we really know how they work? Is there a single common mechanism yet to be identified or can depression be treated by different mechanisms?**

Efficacy of antidepressant drugs – **Are antidepressant drugs that alter the activity of both serotonin and noradrenaline more effective than drugs that affect one alone? Are venlafaxine, milnacipran and mirtazapine of equal efficacy? Are drugs that inhibit the reuptake of noradrenaline more effective than drugs that inhibit the reuptake of serotonin?**

Adverse effects – **Will the probability of discontinuation with the latest drugs be as low as with SSRIs? (Venlafaxine and reboxetine, uncertain. Milnacipran and mirtazapine, probably.) Will post-marketing surveillance identify rare but potentially serious adverse effects?**

Cost – **Will increased competition among newer antidepressant drugs reduce costs?**

The questions in Box 2 are amenable to scientific investigation, and some have been investigated already using older antidepressant drugs. Meta-analysis of antidepressant effects has found that patients with depression who require hospital admission improve more with antidepressant drugs that affect the function of both noradrenaline and serotonin in the brain than with SSRIs (see Anderson, 1997).

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Multiple choice questions

1. The following antidepressant drugs are correctly paired with their mode of action:
   a mianserin – α_2 adrenoceptor antagonism
   b lofepramine – inhibition of noradrenaline reuptake
   c clomipramine – inhibition of noradrenaline and serotonin reuptake
   d reboxetine – inhibition of noradrenaline reuptake
   e mirtazapine – blockade of α_2 - adrenoceptors on noradrenaline- and serotonin-containing neurons.

2. The following statements about antidepressant drug treatment are correct:
   a antidepressant drugs may have many neurochemical effects but they all either inhibit the reuptake of a neurotransmitter or inhibit monoamine oxidase
   b no firm conclusions can be drawn from one or two comparative trials of antidepressants
   c the findings from comparative trials depend little upon whether they are based in general practice or hospital practice
   d there is no credible evidence that tricyclic drugs such as amitriptyline or clomipramine are more effective than SSRIs in severe depression
   e there is accumulating evidence that reuptake inhibitors specific for noradrenaline are more effective than those specific for serotonin.

3. The selection of dose within the recommended range is an important influence on the antidepressant effect of:
   a paroxetine
   b venlafaxine
   c milnacipran
   d reboxetine
   e imipramine.

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4. The existing evidence suggests that the probability of discontinuation because of adverse effects is greater for the following drugs than that observed with fluoxetine:
   a amitriptyline
   b venlafaxine
   c milnacipran
   d reboxetine
   e mirtazapine.

5. The following drugs are correctly paired with their most common adverse effect:
   a fluoxetine – nausea
   b venlafaxine – nausea
   c reboxetine – sedation
   d milnacipran – dysuria
   e mirtazapine – insomnia.

MCQ answers

1	2	3	4	5
a T	a F	a F	a T	a T
b T	b T	b T	b T	b T
c T	c F	c F	c F	c F
d T	d F	d F	d T	d F
e T	e F	e T	e F	e F

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