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Emergency treatment of depression

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Psychiatric emergencies are common and each case presents particular problems and difficulties. This article focuses on one subset of psychiatric emergencies, that of severe depression, and on the role of and use of antidepressant treatments in these conditions. The clinical situations to be discussed in this article include active suicidality, severe psychomotor retardation (with associated problems of hydration and nutrition), affective psychosis, bipolar depression and behavioural disturbance.

All these situations require careful assessment, frequent monitoring and involvement of carers and the multi-disciplinary team. The setting in which treatment should take place and the role of admission, the Mental Health Act, observation and the medical needs of patients with depression in these situations are important, but are beyond the scope of this article. All patients in emergency situations need careful, sympathetic and empathic handling and, on occasions, firm guidance. Supportive psychotherapy is useful, but the use of specific psychotherapeutic techniques in these situations has not been researched. It seems likely that such patients require both the instillation of hope and the skilled challenging of negative thoughts or guilty ruminations. There is a clear need for nursing research on the benefits and utility of such approaches.

Treatments

There is a long-standing view that there is a lag period of 2–3 weeks to a significant benefit of antidepressant treatment compared with placebo. This has been challenged by Parker (1996) who argued that early responses to antidepressants may be obscured by a number of factors inherent in clinical trials. For instance, in clinical trials, a positive treatment effect in some individuals may be obscured by a number of non-responding patients. Parker further argues that in cases where there is no early response, that: "the dose may be insufficient or that particular drug may be ineffective". We would argue that the treatments for which there is evidence of an 'earlier' onset of antidepressant action have in common either early high doses or a broad spectrum of pharmacological activity. Such regimes may induce a more rapid response in a significant proportion of patients if used more commonly.

Electroconvulsive therapy (Box 1)

Although double-blind comparisons with placebo or other antidepressants have not directly addressed the issue of early response, there is evidence to support the widely held clinical impression that electroconvulsive therapy (ECT) often results in a relatively rapid antidepressant effect. How rapid this effect is varies considerably between patients, but a substantial and sustained improvement has been demonstrated after 1–3 treatments (Rodger *et al*, 1994) with nearly maximum improvement in some patients after two weeks of ECT three times a week (Post *et al*, 1987). This makes ECT useful in emergency situations and it seems to work particularly well in situations which are likely to be emergencies, such as psychomotor retardation and psychosis. It has been suggested that it is only effective in these situations (Buchan *et al*, 1992), but more recent evidence has challenged this (Sobin *et al*, 1996), suggesting an early improvement in all subtypes of major depression. It should, therefore, be considered as a possible first-line treatment in all emergency situations.

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Box 1. ECT in emergencies

ECT works well in patients with psychosis or learning disabilities
ECT acts rapidly
Bilateral high-dose therapy three times a week is probably fastest but also causes most cognitive side-effects
Twice-a-week high-dose unilateral treatment is slower but gives an adequate response with fewer cognitive side-effects
ECT is safe in most situations

Stimulation of dopaminergic pathways may give rise to an early antidepressant response, and ECT gives rise to an acute increase in levels of dopamine and its metabolites and an increase in baseline levels following chronic administration. This may be a factor in its rapid onset of antidepressant effect.

The factors that influence speed of response include frequency of administration, electrode placement and electrical dose administered. There is a general consensus that the side-effects of ECT administered more frequently than three times a week outweigh any benefits, even in extreme emergencies. Multiple induction of fits has also been abandoned. The question of whether to give ECT two or three times a week is more difficult. Speed of response is more rapid with ECT treatment three times a week (Shapira *et al*, 1998), but cognitive effects are more severe and there is no difference in final outcome. A three-times-a-week schedule is therefore only indicated in situations where rapid response is particularly crucial. Since treatments early in a treatment course seem to give rise to a proportionally greater degree of improvement than later treatments (Segman *et al*, 1995) there may be logic in giving three treatments in the first week and then reverting to a twice weekly schedule.

There is evidence that bilateral therapy works more quickly than unilateral therapy given an equivalent electrical dose (Sackeim *et al*, 1993). However, the cognitive side-effects of bilateral therapy are more severe. Where unilateral ECT is used, it now appears clear that the 'Lancaster' unilateral electrode position (as demonstrated on old ECT wallcharts) does not achieve sufficiently wide separation of the electrodes. Electrode placement should be in the d'Elia position (d'Elia, 1970) as demonstrated in the *Official Video Teaching Pack* of the Royal College of Psychiatrists' Special Committee on ECT (1994).

The electrical dose necessary to induce a generalised seizure varies considerably between patients (Sackeim *et al*, 1987). There is evidence that it is not the absolute electrical dose administered, but the dose above seizure threshold which is important (Sackeim *et al*, 1993) not only in producing a response, but also in determining the speed of response. Dose titration can be used to determine the seizure threshold. This can be done using a variety of different protocols depending on the type of machine used (Lock, 1995). Sackeim *et al* (1993) showed, in a double-blind placebo-controlled trial, that for both unilateral and bilateral treatment, high-dose therapy resulted in a significantly quicker antidepressant response. In this study, low dose was close to seizure threshold and high dose was 2.5 times seizure threshold. High-dose therapy also resulted in significantly greater cognitive side-effects. There is little evidence regarding speed of response for even higher electrical doses. Low-dose unilateral therapy not only results in a significantly poorer early response, but an overall poor response and despite reduced cognitive side-effects cannot therefore be recommended.

Evidence regarding seizure length is equivocal. Some patients appear to do well despite short seizures, but others do not. Every effort should be made to achieve adequate seizure length (at least 20 seconds) in the emergency situation. In addition, care should be taken to ensure that a seizure occurs at every treatment. This may be a particular problem when patients are being treated with large doses of benzodiazepines for agitation or violence. Long-acting benzodiazepines should be avoided if possible when ECT is being administered. Neuroleptics are generally proconvulsant and therefore better in this situation. Where a hypnotic is required during an emergency course of ECT, we recommend a short-acting hypnotic such as zolpidem (mean half life 2.4 hours) which is unlikely to affect seizure threshold the following morning. If anticonvulsants are being used as mood stabilisers or to augment antidepressant effect, they may need to be discontinued while the ECT is in progress. It should be remembered, however, that the relapse rate is high following ECT and that it may be prudent to recommence these agents as soon as a course is completed. If, despite these measures, adequate fits cannot be induced, caffeine augmentation may be used (Lurie & Coffey, 1990).

Since emergency situations are more common where there is co-existing physical illness, safety of treatment is an important factor. However, with advances in the practise of ECT, it is increasingly possible to treat patients effectively and safely in virtually every situation. The American Psychiatric Association (1990) Task Force on ECT report and the Royal College of Psychiatrists' ECT Handbook (Royal College of Psychiatrists, 1995) cite no

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'absolute contraindications' to ECT. In particular, it has been shown that ECT can be used relatively safely in the elderly, patients with cardiac abnormalities and even during pregnancy.

In summary, ECT is a rapid effective treatment for all forms of depression, but particularly in the emergency situations of psychosis and learning disabilities. It is safe for most patients, including the elderly. Maximum speed of response can be obtained using treatment three times a week, bilateral electrode placement and high-dose electrical stimulation, but this schedule gives rise to greater cognitive side-effects than more conservative schedules. We therefore only recommend this in dire emergencies, for instance when patients are dehydrated, stuporose or extremely suicidal. In less pressing situations we concur with the suggestion of (Lock, 1995) that unilateral ECT in a dose of 100–200% above seizure threshold should be used or, where staff are relatively inexperienced, bilateral ECT in a dose of 50–100% above seizure threshold.

Antidepressant drugs

Antidepressant pharmacotherapy (Box 2)

Most antidepressant medications increase the activity of the serotonergic or the noradrenergic systems in the brain. They frequently also have effects on other transmitter systems. There is a widely held belief that these agents have a time lag of two weeks before they have an effect which is greater than placebo. However, this is based on clinical trials which often do not make repeated early measurements (and there is a dearth of reliable instruments to do this task) and in which an initial improvement in some patients may be masked by a number of non-responders. Various methods of analysis have been employed to attempt to overcome this problem and have been used in attempting to determine which treatments, if any, have an advantage in terms of speed of action. This issue has been well reviewed in a publication by the National Institute of Mental Health (1995). Various pharmacological mechanisms have been suggested which may contribute to delay in onset of antidepressant efficacy. β-adrenoceptor down-regulation occurs in most cases after 2–4 weeks, a time lag which roughly corresponds to the observed onset of action of antidepressant treatments. It has been suggested that this down-regulation may be accelerated by a simultaneous action on both serotonergic and noradrenergic systems (Baron *et al*, 1988). A second suggested mechanism is auto-inhibition by presynaptic 5-HT_{1a} autoreceptors which only down-regulate after chronic treatment with serotonergic agents (Blier *et al*, 1988). This is the basis of strategies such as the use of the 5-HT_{1a} antagonist pindolol to accelerate response. It is now known that there are several other changes in receptor sensitivity which occur with chronic antidepressant therapy and it seems unlikely that a single mechanism is involved.

Venlafaxine blocks dopamine reuptake, resulting in increased levels of dopamine and its metabolites, similarly to ECT. Psychostimulants such as amphetamine or methylphenidate give rise to a transient elevation of mood in a high proportion of patients with depression. There is no evidence that they are effective antidepressants and we would not recommend their use. Similarly L-dopa has proved ineffective apart from promoting a degree of psychomotor activation.

Box 2. Antidepressants in emergencies

- Clomipramine and venlafaxine appear to induce an early antidepressant response when high doses are reached early in treatment
- Pulse loading may make early high-dose clomipramine more tolerable but there is no clear advantage of the intravenous route
- The mechanism of this early response is not clear; action on both noradrenergic and serotonergic systems may reduce the number of non-responders
- Both have proven efficacy in severe depression

Tricyclic antidepressants

Tricyclic antidepressants (TCAs) have traditionally been the mainstay of acute antidepressant therapy. Claims of a rapid onset of action may often be due to a reduction in the Hamilton Rating Scale for Depression (HDRS; Hamilton, 1960) score due to sedation. None the less, this side-effect may be particularly useful in agitated depression. The speed of action of TCAs may, however, be reduced if side-effects necessitate slow titration to an adequate dose. They should be used with extreme care in patients at risk of suicide, because of their toxicity in overdose.

It has been claimed that clomipramine may have a rapid onset of action, particularly when administered intravenously. The rationale behind this is to avoid the extensive first-pass metabolism, which occurs with TCAs, and thereby achieve an adequate concentration more quickly. Closer examination of the evidence reveals that early oral administration

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of high doses may well achieve the same aim. Three double-blind trials of intravenous versus oral clomipramine have shown no differences in either response or side-effects. In one of these, patients received two doses of clomipramine (150 mg then 200 mg 24 hours later). Continuous treatment was not initiated for five more days (Pollock *et al*, 1989). The mean HDRS score, five days after pulse-loading, had dropped by 35% (range 13.3% to –82.4%). Relatively high concentrations of antidepressant were achieved in this study at an early stage, which may be the crucial factor. Genuine double-blind placebo-controlled trials of intravenous clomipramine are clearly difficult since the immediate side-effects will make it apparent which treatment is being taken and thereby unblind patients. The only recent study to attempt this involved only 16 adolescents and did not adequately address this issue (Sallee *et al*, 1989).

Similar claims have been made of an early response to venlafaxine which has, in common with clomipramine, a combined serotonergic and noradrenergic action. It also gives rise to early down-regulation of β-adrenoceptors. Once again, evidence suggests that a rapid response may only occur when the dose is rapidly escalated. In hospitalised patients with melancholic depression, the response to venlafaxine with doses rapidly escalating to 375 mg/day over five days was compared with the response to imipramine 200 mg (reached over five days; Benkert *et al*, 1996). The response was significantly faster as judged by the HDRS but not by the Montgomery–Åsberg Depression Rating Scale (MADRS; Montgomery & Åsberg, 1979). Another study compared venlafaxine with placebo in hospitalised patients with melancholic depression. High doses of venlafaxine averaging 350 mg/day were used. Venlafaxine provided significantly greater improvement in the MADRS scores after four days and in the HDRS scores after one week than did placebo. It also seems likely that the improvement was clinically significant (Guelfi *et al*, 1995). Further trials in out-patients also demonstrate a consistent early response using a number of different methods of analysis (Derivan *et al*, 1995). Their robust action in in-patients with severe depression make clomipramine and venlafaxine good candidates in emergencies, especially when ECT is not being considered. Rapid escalation to high dose seems necessary for a rapid response and this is more likely to be tolerated with venlafaxine.

Selective serotonin reuptake inhibitors

There is no consistent evidence of a rapid response to selective serotonin reuptake inhibitors (SSRIs). Several important issues must be addressed in their use in emergencies. The first of these is whether they reduce suicide. SSRIs are safer in overdose, but it has been argued that decreased effectiveness in cases of severe depression may increase the rate of suicide by other means. Whether or not SSRIs are less effective in severe melancholic depression is not clear. A meta-analysis of 55 double-blind studies (Anderson & Tomenson, 1994) found some suggestion of a better response to TCAs in patients with severe depression. In particular, a comparison of paroxetine with clomipramine (Danish University Antidepressant Group, 1990) showed a better response with clomipramine and this study accounted for most of the difference. Clerc *et al* (1994) also showed a better response to venlafaxine than fluoxetine in hospitalised patients with DSM–III–R (American Psychiatric Association, 1987) major depression with melancholia. It is notable that the comparison drugs in these two studies may be more efficacious than other tricyclics because of their potent serotonergic and noradrenergic action. Other studies of SSRIs compared with other TCAs have not found such a difference and, in fact, some have found an advantage of SSRIs over TCAs in severe depression (Anderson & Tomenson, 1994). The research is complicated by different definitions of severity and further work is required before a firm conclusion can be drawn.

In out-patients, discontinuation because of side-effects may be a more potent cause of treatment failure and there is some evidence that this is more common with TCAs than SSRIs (Martin *et al*, 1997). The reported inverse relationship between indices of central serotonin (5-HT) function and indices of impulsivity in human subjects suggests the possibility that enhancement of 5-HT activity with SSRIs and related drugs reduces impulsive behaviour. This may reduce anger, irritability and suicidality in patients with depression. Although several open studies suggest that SSRIs may be useful in controlling anger attacks in subgroups of patients with depression in whom this is a problem, the only double-blind placebo-controlled trial so far conducted showed no significant difference between placebo and either active agent, and no difference between sertraline and imipramine (Fava *et al*, 1997). Therefore, the superiority of SSRIs in managing impulsive anger is not demonstrated. Likewise, there is no direct evidence that SSRIs specifically reduce the likelihood of impulsive suicide or parasuicide.

Combinations

The possible biological explanations for delay in antidepressant onset have led to at least two clinical strategies. Evidence that the combination of

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desipramine and fluoxetine leads to a rapid down-regulation of β-adrenoceptors led to a trial of these agents clinically and the suggestion that there was an early clinical response (Nelson *et al*, 1991). This has not yet been demonstrated in a double-blind trial. The combination has also been tried in treatment-resistant depression with equivocal results. There are inherent difficulties in the co-prescription of TCAs and SSRIs as the latter may inhibit tricyclic metabolism giving rise to large increases in TCA blood levels (Nemeroff *et al*, 1996). Pharmacodynamic interactions may also be a problem. If this strategy is to be used effectively in the acute situation, close monitoring of side-effects and TCA blood levels is necessary. The net effect of this combination may be mimicked by the use of antidepressants with combined serotonergic and noradrenergic activity, without the problem of unpredictable interactions.

Augmentation of SSRIs with pindolol has been suggested as a way of overcoming 5-HT_{1a}-mediated autoinhibition (Artigas *et al*, 1996). This has shown promising results in open label studies but placebo-controlled trials are currently conflicting. There is evidence that beta-blockers may actually cause depression (Avorn *et al*, 1986). This strategy cannot currently be recommended in emergency situations.

Special situations

Psychotic depression

In the Epidemiologic Catchment Area (ECA) Study (Johnson *et al*, 1991), 14% of subjects who met criteria for major depression had a history of psychotic features. Psychotic symptoms may increase the distress of depression and the risk of suicide may be greater in psychotic than non-psychotic depression (Roose *et al*, 1983). Prompt, effective treatment is therefore necessary. As discussed previously, in true emergencies, ECT is usually the treatment of choice because of its demonstrated speed of action. There has been no published double-blind study comparing ECT and combination antidepressant/antipsychotic treatment prospectively. A meta-analysis of individual studies published from 1959 to 1988 (Parker *et al*, 1992) found ECT to be superior to the combination of antidepressant and antipsychotic medications but different ECT schedules were compared with several different combinations, dosages and durations of medication and the speed of onset was not compared.

Most clinicians would agree that antipsychotics are useful in reducing the acute distress of psychotic depression. There is also good evidence of an advantage in terms of overall response. Several studies have demonstrated a response to the combination of a TCAs and a neuroleptic agent after there had been no response to a TCA alone. Spiker *et al* (1985) compared the combination of amitriptyline and perphenazine, amitriptyline alone and perphenazine alone in the treatment of patients with psychotic depression over a five-week period. Seventy-eight per cent of 18 patients treated with the combination responded in contrast to 41% of 17 patients treated with amitriptyline and 19% of 16 patients treated with perphenazine. Seven of the 13 patients who failed to respond to perphenazine were not psychotic at the completion of the study but were still depressed. Atypical antipsychotics, which include central D_2-like and 5-HT_2 receptor antagonist properties should in theory be of therapeutic value in patients with psychotic and depressive symptoms. However, despite encouraging case studies, no double-blind trial has been carried out.

It has been suggested that particularly high doses of neuroleptics may be necessary in psychotic depression. In an open study (Nelson *et al*, 1986), there was a significantly better outcome in a small group of patients taking the equivalent of 45 mg/day perphenazine compared with patients taking less than 32 mg/day. However, we would suggest that higher doses be reserved for treatment-resistant, not emergency, cases.

We would suggest that antipsychotic medication should be used in most cases of acute psychotic depression. When antipsychotic agents are used, care should be taken to monitor for the possible side-effect of akathisia, which has been shown to increase violence (Crowner *et al*, 1990) and possibly also suicide (Sachdev & Longragan, 1991). This may be a particular problem if antipsychotics are used in combination with serotonergic agents. Care should also be taken when neuroleptics are co-prescribed with antidepressants which inhibit the metabolism of the neuroleptics by the hepatic cytochrome P450 enzyme system. All the SSRIs except fluvoxamine and citalopram are potent inhibitors of cytochrome P450 2D6. Plasma levels of haloperidol have been found to be elevated following the addition of fluoxetine. Fluvoxamine is a potent inhibitor of cytochrome P450 1A2 and has been associated with increased serum concentrations of haloperidol and clozapine (Nemeroff *et al*, 1996).

Psychomotor retardation and stupor

Electroconvulsive therapy works particularly well in this situation especially where patients are unable

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to take oral medication. Particular attention should be paid to hydration and to the avoidance of complications such as chest infection, dental sepsis, decubitus ulcers and deep vein thrombosis. Intravenous fluids may be necessary.

Where stupor occurs, a history of development of this from a state of psychomotor retardation is often available. If no such history is available, the diagnosis should be reviewed regularly. The differential diagnosis in cases of stupor includes schizophrenia, hysteria and organic causes.

Suicidality

Fawcett *et al* (1990), in a controlled follow-up study of suicide in major affective disorder, reported the following risk factors for suicide within one-year: anxiety, panic, insomnia, anhedonia, loss of concentration and alcohol misuse, and for suicide after one-year parasuicide and hopelessness. In addition, patients with stated intent are almost certainly at increased risk and the early morning may be a particularly risky time.

Three points are important when considering treatment. First, clinical experience suggests that early reduction in psychomotor retardation, in severe depression, may give patients the motivation which allows them to act on suicidal impulses or plans. Extreme vigilance should therefore be exercised in this early phase of treatment. Second, as mentioned above, akathisia should be carefully looked for.

Finally, it should be emphasised that studies have, in the past, shown that patients with a history of depression who have committed suicide, have often been taking inadequate doses of antidepressants (Myers & Neal, 1978). We would emphasise the importance of identifying patients at risk of suicide and treating vigorously with either ECT or an adequate dose of antidepressant, reached early in the course of treatment (see Box 3).

Box 3. Risk factors for suicide in depressive illness

Inadequate treatment
Anxiety, panic, insomnia, anhedonia, loss of concentration, alcohol misuse
Parasuicide, hopelessness
Akathisia
Activation early in treatment

Bipolar depression

Although bipolar depression is a frequent clinical problem, double-blind studies of its treatment are scarce. There is evidence that antidepressants induce mania and also that they may contribute to cycle acceleration in approximately one-quarter of patients (Altshuler *et al*, 1995). Therefore, in non-urgent situations it is usually best to avoid antidepressants, particularly in high doses. Fluoxetine may be particularly problematic because of its long half-life. Depending on the history it may be possible to contain disturbance with symptomatic treatment while treating with a mood stabiliser. However, in cases of learning disability, psychosis, suicidality or extreme distress, some form of treatment is necessary. There is preliminary evidence that carbamazepine, sodium valproate, lamotrigine and gabapentin have an antidepressant effect (Post *et al*, 1996).

There is no clear evidence regarding rates of ECT-precipitated mania. Electroconvulsive therapy may be a good alternative in severe bipolar depression since it is also effective in treating mania. If mania is precipitated, many clinicians simply continue the course of ECT. However, we would advocate caution in the use of ECT since the overall effect on outcome is not known and there is not currently good evidence regarding the effect of ECT on cycle length.

It should also be remembered that depression during mania (dysphoric mania) may be a particularly serious situation since the risk of suicide appears to be much higher (Dilsaver *et al*, 1994). Antidepressants are not likely to be helpful in this situation and lithium appears to be substantially less effective than sodium valproate (Swann *et al*, 1997), which may be the treatment of choice.

Behavioural disturbance

The management of the acutely disturbed patient has been well reviewed elsewhere in this journal (Macpherson *et al*, 1996). Little has been written specifically on the issue of the acutely disturbed or violent depressed patient, but the principles of management are essentially the same. The two main classes of agents used as adjuncts to antidepressant therapy are neuroleptics and benzodiazepines. When a course of ECT is being prescribed, long-acting benzodiazepines may interfere with treatment and are therefore best avoided. There is no evidence that short-acting benzodiazepines cause behavioural disinhibition in agitated depression and they are often useful adjuncts to treatment. Neuroleptics are certainly indicated where there is psychosis.

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Conclusions

Although many factors may give rise to a degree of urgency in treating depression, a relatively small range of treatments is appropriate. We have reviewed these in particular with regard to their efficacy in severe depression and their speed of action.

Electroconvulsive therapy remains the treatment of choice in many emergency situations and research is increasingly refining its practice and safety. Antidepressant medication is limited by a therapeutic delay but this may be overcome by early use of high doses and agents with a broad spectrum of pharmacological efficacy. The use of adjunctive medication such as benzodiazepines and neuroleptics may be beneficial, but careful monitoring for interactions and adverse effects is particularly important.

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Multiple Choice Questions

1. Electroconvulsive therapy:
   a is ineffective in agitated depression
   b acts faster if given three times a week than if given twice a week
   c gives rise to worse cognitive side-effects when given unilaterally than bilaterally
   d is particularly effective in psychotic depression.

2. An early antidepressant response:
   a may be related to stimulation of dopaminergic pathways
   b may occur with high-dose venlafaxine
   c may be obscured in clinical trials by non-responders
   d always occurs if pindolol is added to an antidepressant.

3. In bipolar affective disorder:
   a antidepressants should be avoided if possible
   b carbamazepine may have an antidepressant effect in depressive episodes
   c lithium is particularly effective in dysphoric mania
   d the risk of suicide in dysphoric mania is low.

4. In psychotic depression:
   a there is no additional benefit in adding an antipsychotic to antidepressant therapy
   b akathisia is a potentially serious side-effect
   c there are no potential interactions between antidepressants and antipsychotics
   d suicide is more common in the evening than the morning.

MCQ answers

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

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