

IV. Medications and Other Biological Treatments

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Background: The Canadian Psychiatric Association and the Canadian Network for Mood and Anxiety Treatments partnered to produce clinical guidelines for psychiatrists for the treatment of depressive disorders.

Methods: A standard guidelines development process was followed. Relevant literature was identified using a computerized Medline search supplemented by review of bibliographies. Operational criteria were used to rate the quality of scientific evidence, and the line of treatment recommendations included consensus clinical opinion. This section, "Medications and Other Biological Treatments," is 1 of 7 articles that were drafted and reviewed by clinicians. Revised drafts underwent national and international expert peer review.

Results: Evidence-based recommendations are presented for 1) choosing an antidepressant, based on efficacy, tolerability, and safety; 2) the optimal use of antidepressants, including augmentation, combination, and switching strategies; 3) maintenance treatment; and 4) electroconvulsive therapy (ECT), light therapy, and additional somatic treatments. Evidence from metaanalyses is presented first, followed by conclusions from randomized controlled trials (RCTs) and, if appropriate, open-label data.

Conclusions: There is significant evidence to support the role of selective serotonin reuptake inhibitors (SSRIs), novel agents, and classic agents in the treatment of major depressive disorder (MDD). There is also evidence to support the use of somatic treatments, including ECT and light therapy, for some patients with MDD. There is limited evidence for the use of specific medications to treat subtypes of MDD. There is emerging evidence to support augmentation and combination strategies for patients previously nonresponsive to medication.

INTRODUCTION

In an ideal world, specific patient profiles would determine specific antidepressant treatments. To date, the evidence from randomized controlled trials (RCTs) for such targeted pharmacotherapy is limited. Many variables are likely to influence the outcome of treatment, including the population under investigation (for example, subtypes within major depression, inpatient or out patient status, severity, age, sex, culture, or comorbid psychiatric and medical illness), the duration of treatment (acute or maintenance), and clinical trial conditions (for example, placebo-controlled, active-drug comparison, or both).

The interpretation of data may also be influenced by how outcome is defined. The generally accepted measure of response is a 50% reduction in symptoms (usually on a 17-item Hamilton Depression Rating Scale [HDRS]); this is the accepted

standard for approval of antidepressants by regulatory bodies. Remission, on the other hand, requires a nearly complete level of symptom reduction; this has been applied as an outcome criterion in recent trials (1,2).

Most evidence-based recommendations are derived from relatively brief acute pharmacotherapy trials involving carefully selected adult patients with various phenotypes of major depressive disorder (MDD). In most instances, these are monotherapy trials, with significantly fewer studies of augmentation and combination strategies. Despite these limitations, there has been an increasing tendency to prescribe polypharmacy for patients with depression (3). More recently, evidence for maintenance of efficacy up to at least 1 year has been a regulatory requirement for newer antidepressant agents.

The goal of this section is to provide the clinician with evidence-based recommendations for (1) choosing an antidepressant based on efficacy, tolerability, and safety; (2) optimal use of antidepressants, including augmentation, combination, and switching strategies; (3) maintenance treatment; and (4) other biological treatments, including electroconvulsive therapy (ECT), light therapy, and other somatic treatments. Evidence from metaanalyses is presented first, followed by conclusions from RCTs and, if appropriate, open-label data.

CHOOSING AN ANTIDEPRESSANT

Clinicians have 3 major classes of antidepressants to choose from. Classic agents, mainly tricyclic and other heterocyclic antidepressants (TCAs) including amitriptyline, amoxapine,

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Table 4.1 Pharmacokinetics and dosing of selective serotonin reuptake inhibitors (SSRIs) and novel antidepressants^a

Medication	Usual Effective Dosing (mg daily)	Range (mg daily)	Biotransformation Pathways	Half-life	Protein Binding
SSRI					
Citalopram	20–40	10–60	Demethylation in 2 steps involves CYP2C19, 2D6 and 3A4	37 hrs	80%
Fluoxetine	20–40	10–80	Demethylation involves CYP2D6	4–6 days	95%
Fluvoxamine	100–200	50–300	Demethylation and deamination involves CYP2D6 and 1A2	17–22 hrs	80%
Paroxetine	20–40	10–60	Oxidation and Demethylation involves CYP2D6	24 hrs	95%
Sertraline	50–100	50–200	Demethylation involves CYP3A4	25–26 hrs	98%
Novel					
Bupropion SR	150–300	150–300 (divided dose)	Hydroxylation involves CYP2B6	21 hrs	84% (parent)
Mirtazapine	15–45	15–45 (single dose)	Demethylation and hydroxylation involve CYP2D6, 1A2 and 3A4	20–40 hrs (parent)	85% (parent)
Nefazodone	300–500	300–500 (divided dose)	Dealkylation and hydroxylation involve CYP3A4 and 2D6	1.5–4 hrs (parent) 2–4 hrs (HO-Hef 18–33 hrs (TAD) 4–9 (mCPP)	99% (parent)
Reboxetine ^b	4–8	4–10 (divided dose)	Dealkylation and hydroxylation involve CYP3A4	13 hrs (parent)	97% (parent) α -1-acid glycoprotein > albumin
Venlafaxine IR/XR	75–225	37.5–375	O-desmethylation involves CYP2D6 and others	5–7 hrs (parent) 11–13 hrs (ODV)	27% (parent) 30% (ODV)

^aAdapted from Canadian Pharmaceutical Association. Compendium of Pharmaceuticals and Specialties. Toronto, Canadian Pharmaceutical Association, 2001; and Kent JM. SNARIs, NaSSAs, and NaRIs: new agents for the treatment of depression. *Lancet* 2000; 355:911–8. ^bNot currently available in Canada.

clomipramine, desipramine, doxepin, imipramine, maprotiline, nortriptyline, protriptyline, and trimipramine, as well as monoamine oxidase inhibitors (MAOIs)—phenelzine and tranylcypromine—continue to be favoured in treatment-refractory cases. Selective serotonin reuptake inhibitors (SSRIs)—citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline—have been a leading class throughout the 1990s and are considered first-line agents today. Novel agents (non-TCA agents with noradrenergic or mixed actions), including bupropion, mirtazapine, moclobemide, nefazodone, reboxetine, trazodone, and venlafaxine represent an alternative class of agents. Reboxetine is not routinely available in Canada as of June 2001. Details of dosing and metabolism for SSRIs and novel agents are presented in Table 4.1.

Although this classification can legitimately be challenged, particularly in terms of serotonin selectivity among the SSRIs, it is a framework from which to develop guidelines for the use of antidepressants. Cornerstones in the decision-making process are effectiveness (usually inferred from RCT efficacy data), tolerability (side-effect profiles), and safety.

1. How do SSRIs and novel agents compare with classic agents and with each other in the treatment of MDD?

Several metaanalyses have demonstrated comparable efficacy between SSRIs and TCAs (4–9). One metaanalysis, while finding no differences between individual SSRIs and TCAs, noted a slight advantage to TCAs in a subgroup of patients with high HDRS scores (10). Following Danish reports that clomipramine was more effective than citalopram,

paroxetine, and moclobemide in the treatment of hospitalized patients (11–13), a metaanalysis of studies of inpatients with depression found that amitriptyline was significantly more effective than comparator SSRIs, although a sensitivity analysis involving larger studies (100 subjects) reduced any TCA advantage to a nonsignificant trend (14). These results were essentially confirmed in an updated metaanalysis (4). It should be noted, however, that another metaanalysis found that paroxetine is equivalent to TCAs in hospitalized patients with depression (15).

For each of the novel agents, there are also metaanalyses and/or replicated RCTs demonstrating efficacy comparable to TCAs although they have not been subject to the same level of metaanalytic rigour (9,16–18). Recent studies have focused on mode of action of novel antidepressants and relative efficacy. A metaanalysis of 105 studies did not find any relationship between postulated mechanism of action of antidepressants (serotonin or norepinephrine reuptake inhibition, 5-HT₂ antagonism, or various combinations of these effects) and relative efficacy (19). Metaanalyses involving venlafaxine studies found greater response and remission rates for venlafaxine, compared with SSRIs (20,21). The remission rates for SSRIs in these comparison studies are however, generally much lower than those reported in other SSRI trials (22,23). Hence, this issue remains controversial.

Another relevant issue in these comparisons is dosing. There is evidence that antidepressants such as venlafaxine may involve different modes of action at different dosages (24). A metaanalysis failed, however, to demonstrate a dosage–response relation when individual drug dosages were converted to imipramine equivalents, and no advantage was found for dosages above the equivalent of imipramine 100 to 200 mg

daily (25). Methods used to establish dosing equivalence across antidepressants may be questionable and may account for these negative findings.

In the absence of clear and significant differences in efficacy, the choice of medication must be individualized for a particular patient. Subsequent questions will address both patient and treatment factors, including subtype and severity of depression, tolerability and safety, and sequenced approaches to treatment. Refer to Section V for combined psychotherapy–pharmacotherapy recommendations; Section VI for specific influences of age, sex, and culture on treatment; and Section VII for the treatment of depression associated with comorbid physical and psychiatric conditions.

Recommendations for Treatment of Major Depressive Disorder (see Table 4.6)	
First-line treatments	• Selective serotonin reuptake inhibitors (SSRIs) and novel agents (Level 1 evidence). • Venlafaxine may have higher remission rates than SSRIs (Level 1 evidence).
Second-line treatments	• Amitriptyline and clomipramine have greater efficacy than SSRIs in hospitalized patients with depression (Level 2 evidence). Safety and tolerability issues however, need to be considered.
Third-line treatments	• Other tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs), because of safety and tolerability issues (Level 2 evidence).

2. How does the subtype of depressive disorder influence selection of treatment?

MDD with Atypical Features

Based on RCTs, phenelzine was superior to imipramine, which in turn was superior to placebo (26,27). Fluoxetine and imipramine were equally effective, and both were superior to placebo, although fluoxetine was better tolerated (28). Sertraline and moclobemide were also effective for atypical depression, although sertraline-treated patients had a significantly greater degree of improvement on several psychosocial and efficacy parameters (29).

Recommendations for Treatment of Major Depressive Disorder with Atypical Features (see Table 4.6)	
First-line treatments	• Fluoxetine, moclobemide, sertraline (Level 2 evidence).
Second-line treatments	• Phenelzine (Level 2 evidence).
Third-line treatments	• Imipramine (Level 2 evidence).

MDD with Melancholic Features

Most patients who meet additional criteria for melancholia also have high levels of severity, but not all patients with “severe depression” (for example, HDRS score > 24) necessarily

have melancholic features. There is also an overlap between hospitalized (inpatient) depression and melancholia (30).

In metaanalyses, paroxetine (15), moclobemide (16), and venlafaxine (31) were significantly more effective than placebo in treating patients with melancholia; they were similar in efficacy to TCA comparators. Both citalopram (32) and fluoxetine (33) were superior to placebo in outpatients with melancholia. Danish studies, however, found that for hospitalized patients, most with melancholic features, remission rates were significantly higher with clomipramine compared to paroxetine, citalopram, and moclobemide (11–13). Venlafaxine also had higher remission rates, compared with fluoxetine in some (34), but not all (35), studies of patients with melancholia. Nortriptyline was also significantly more effective than fluoxetine in a sample of mostly older patients with melancholia and concurrent cardiovascular disease (70%) (36). Further review supports the superiority of TCAs over SSRIs in melancholic depression (37), although toxicity and compliance issues lower the recommendation for TCAs.

Recommendations for Treatment of Major Depressive Disorder with Melancholic Features (see Table 4.6)	
First-line treatments	• Paroxetine, venlafaxine (Level 1 evidence).
Second-line treatments	• Tricyclic antidepressants (TCAs), moclobemide (Level 1 evidence).
Third-line treatments	• Citalopram, fluoxetine (Level 2 evidence).

MDD with Psychotic Features (Delusional Depression)

Few RCTs were specifically designed to evaluate efficacy in psychotic or delusional depression, and there are no placebo-controlled studies. Most of the studies compare mixed psychotic and nonpsychotic depression cohorts who received naturalistic treatment. The combination of amitriptyline plus perphenazine was significantly superior to either alone (38). A metaanalysis found that ECT was significantly superior to TCAs alone (39). However, only a trend was found for greater efficacy of ECT over combination (TCA plus antipsychotic) therapy, with bilateral ECT distinctly more effective than unilateral. There was also a trend toward combination TCA/antipsychotic treatment being more effective over either medication alone. Results of this metaanalysis are limited by the inclusion of open-label trials. Fluvoxamine alone or in combination with pindolol may be effective for psychotic depression (40). The same group reported that sertraline was significantly more effective than paroxetine (41), although conclusions were limited by extremely high drop-out rates in the paroxetine group. Most studies used the older, typical antipsychotic medications. Emerging evidence from open-label studies in psychotic depression supports the use of newer atypical antipsychotic medications (for example, olanzapine [42]) in combination with antidepressants. Thus, even though there are few data for the atypical

antipsychotics (olanzapine, quetiapine, and risperidone), they should be considered in combination treatments for psychotic depression.

Recommendations for Treatment of Major Depressive Disorder with Psychotic Features (see Table 4.6)	
First-line treatments	Electroconvulsive therapy (ECT) or an antipsychotic plus antidepressant (Level 1 evidence).
Second-line treatments	Olanzapine plus an antidepressant (Level 3 evidence).
Not recommended	Monotherapy with selective serotonin reuptake inhibitors (SSRIs) (despite Level 2 evidence that there is limited clinical support).

MDD with Seasonal Pattern

Clinical guidelines (43) have now been published for seasonal affective disorder (SAD), equivalent to seasonal pattern specifier in DSM-IV. Metaanalyses and replicated RCTs have shown that light therapy is effective in treating SAD (see question 20). There are fewer medication studies. RCTs show that fluoxetine and moclobemide are effective (44–46), while bupropion (47), citalopram (48), and tranylcypromine (49) were beneficial in open trials. Comparative studies between light therapy and antidepressants are not yet completed, so choice of treatment depends on patient preference and other clinical factors, including comparative side effects, severity of depression, presence of atypical features, and motivation for treatment (43).

Recommendations for Treatment of Major Depressive Disorder with Seasonal Pattern (see Table 4.6)	
First-line treatments	Bright-light therapy (Level 1 evidence).
Second-line treatments	Fluoxetine, moclobemide (Level 2 evidence).
Third-line treatments	Bupropion, citalopram, tranylcypromine (Level 3 evidence).

“Anxious” Depression

Although “anxious” depression is not a subtype of MDD within DSM-IV (50), 60% to 90% of individuals with a primary diagnosis of depression also experience symptoms of anxiety (51). Individuals with depression who suffer from significant anxiety have more severe depressive symptomatology, greater functional and psychosocial impairment, and poorer prognosis following treatment, compared with individuals with depression and low levels of anxiety (51,52).

In 3 metaanalyses, moclobemide (53), mirtazapine (54), and venlafaxine (52) were as effective as active comparators (imipramine, amitriptyline, and trazodone) and superior to placebo. Paroxetine (55) and sertraline (56) were as effective as clomipramine, while fluvoxamine and lorazepam (57) were comparable in efficacy. Other studies (58,59) also

support the efficacy of paroxetine in reducing symptoms of anxiety associated with depression. Clonazepam augmentation of fluoxetine was superior to fluoxetine alone in the first 3 weeks of a double-blind trial (60).

Recommendations for Treatment of “Anxious” Depression (see Table 4.6)	
First-line treatments	Mirtazapine, moclobemide, paroxetine, sertraline, venlafaxine (Level 1 evidence).
Second-line treatments	Amitriptyline, fluvoxamine, imipramine, trazodone (Level 1 evidence).
Not recommended	Lorazepam or other benzodiazepines are not recommended as monotherapy, due to concerns about dependency, but may be used as short-term adjunctive therapies (Level 2 evidence).

Chronic Depression/Dysthymic Disorder

From a clinical perspective, patients with pure dysthymia and those who meet diagnostic criteria for double depression (61) are often indistinguishable. The duration of symptoms may be as long as 30 years prior to treatment. Although the number of RCTs in dysthymia is limited, there is general agreement that active pharmacological treatments are more effective than placebo in the short-term treatment of patients with dysthymia (62,63). A metaanalysis confirmed the equivalent efficacy of TCAs, SSRIs (fluoxetine and sertraline), MAOIs, and other agents, including moclobemide and ritanserin (64). TCAs were associated with more adverse events and higher drop-out rates. There were no significant differences in rates of response between patients with pure dysthymia and those with double depression, suggesting that such differentiation may not have any treatment implications.

In individual RCTs, sertraline is the most investigated SSRI (65,66). Paroxetine was superior to placebo in patients aged 60 years or over who were treated in primary care settings (67). Overall, data from RCTs suggest no difference in dose range, frequency of adverse effects, or placebo response between dysthymia and major depression subjects. In open-label studies, venlafaxine (68) and mirtazapine (69) were effective.

Chronic depression is one condition in which combined pharmacotherapy and psychotherapy may produce superior results (70) (see Section V).

Recommendations for Treatment of Chronic Depression/Dysthymic Disorder (see Table 4.6)	
First-line treatments	Fluoxetine, fluvoxamine, moclobemide, nefazadone, paroxetine, sertraline (Level 2 evidence).
Second-line treatments	Desipramine, imipramine (Level 2 evidence).
Third-line treatments	Mirtazapine, venlafaxine (Level 3 evidence).

Subthreshold Depressions

Proposed criteria for several additional subthreshold depressive disorders, including minor depressive disorder and recurrent brief depression, are listed in DSM-IV Appendix B (50). There are currently limited data on optimal treatments for these disorders. For a review of premenstrual dysphoric disorder (PMDD) see Section VI.

Minor Depressive Disorder

Minor depressive disorder describes a subtype of depressive disorder with the same symptoms and duration as major depression, but the symptoms are fewer in number. It remains an elusive category that is poorly characterized in both clinical practice and in research studies. Remarkably high response rates to paroxetine, and slightly lower rates to maprotiline, were reported (71). Paroxetine and problem-solving treatment were both superior to placebo in a primary care setting, in patients aged 60 years or older (67). In an open-label trial, fluvoxamine was associated with a significant decrease in depressive symptomatology and improvement in psychosocial impairment (72).

Recommendations for Treatment of Minor Depressive Disorder (see Table 4.6)	
First-line treatments	Paroxetine (Level 2 evidence, based on individuals aged 60 years and older).
Second-line treatments	- Fluvoxamine (Level 3 evidence). - Maprotiline (Level 2 evidence).

Recurrent Brief Depression

In recurrent brief depression, the number and severity of symptoms are comparable with MDD and last at least 2 days but less than 2 weeks. Based on small RCTs, fluoxetine and paroxetine were not superior to placebo in either decreasing rate of recurrence or suicide-attempt rate (73,74). Although case reports support the use of tranylcypromine (75) and mirtazapine (76), controlled studies are required.

Recommendations for Treatment of Recurrent Brief Depression (see Table 4.6)	
Not recommended	No available evidence for antidepressant treatment.

3. What are the differences in side effects across antidepressants?

There are no multiple-drug, placebo-controlled studies comparing side effects. Therefore, comparative rates usually represent a composite of clinical trials involving different methods of side-effect reporting that may not accurately

capture the side-effect profiles of drugs in long-term use in standard clinical practice. Anticholinergic and cardiovascular side effects are most prevalent with TCAs, especially in the elderly (see Section VI), while gastrointestinal and other side effects are more problematic with SSRIs and other novel agents. Recent data suggest that sexual dysfunction and weight change have been underreported during antidepressant treatment. A detailed frequency comparison of side effects associated with older and newer antidepressants is presented in Tables 4.2a, 4.2b, and 4.2c (adapted from [77]).

Sexual Dysfunction

Until recently, information about sexual side effects has not been systematically evaluated in clinical trials. There are no metaanalytic studies in this area. There is, however, evidence to suggest that drug-related sexual dysfunction is more frequent in men (78,79). TCAs such as imipramine reduced sexual interest in men more than in women (80), while enjoyment and ability to achieve orgasm were more severely impaired with phenelzine than imipramine (81). Controlled studies show that 30% to 50% of patients on SSRIs experience impairment of desire and orgasm (79,82,83), while bupropion (84–86), nefazodone (87), and moclobemide (88) cause significantly less dysfunction. Large uncontrolled studies also suggest that bupropion (89) and moclobemide cause less sexual dysfunction than do SSRIs, while venlafaxine appears to be intermediate in its effects on women (79). Mirtazapine also appears to be relatively free of sexual side effects (90). Some of the sexual side effects of SSRIs have been used therapeutically. For example, SSRIs have been shown to delay ejaculation time in men with premature ejaculation (91).

Conclusions About Sexual Dysfunction During Antidepressant Treatment (see Table 4.6)	
- Low rates of sexual dysfunction (10%) are reported with bupropion, moclobemide, and nefazodone (Level 2 evidence). - Intermediate rates of sexual dysfunction (10% to 30%) are reported with venlafaxine (Level 3 evidence). - Moderate rates of sexual dysfunction (approximately 30% to 50%) are reported with selective serotonin reuptake inhibitors (SSRIs) (Level 1 evidence).	

Weight Gain

Weight change has not been a primary outcome measure of most antidepressant studies. Weight gain during treatment with TCAs (particularly amitriptyline, imipramine, and trimipramine) is well recognized (92–94). Up to 15% of imipramine-treated individuals will experience weight gain (> 5 kg) after 16 weeks. Studies of 6-month duration suggest that TCA-induced weight gain approximates 1 kg per month. Acute-treatment trials employing SSRIs are frequently associated with modest reductions in weight (95). There is, however, no evidence from maintenance studies that weight loss

is sustained with SSRIs. In fact, there is conflicting evidence regarding weight gain during maintenance treatment (95,96). Nefazodone has been shown through acute and maintenance studies to be weight-neutral (97). Bupropion SR appears to be weight-neutral or weight loss-inducing in a dosage-dependent fashion, with up to 25% of patients losing 2.5 kg or more in short term trials (98). Short-term trials also suggest that venlafaxine is weight-neutral; however, there is an absence of controlled, long-term weight data (97).

Moclobemide-treated patients appear to be at low risk of weight gain in acute trials and its weight-gain potential is lower than that of conventional MAOIs (99–101). Mirtazapine exhibits significantly greater weight gain than does placebo in short-term trials, which may be in part due to its histaminergic affinity (102).

Conclusions about Weight Gain During Antidepressant Treatment

(see Table 4.6)

- Selective serotonin reuptake inhibitors (SSRIs), bupropion, moclobemide, nefazodone, and venlafaxine are weight-neutral during the acute phase of treatment (Level 2 evidence).
- Mirtazapine results in weight gain of greater than 7% of body weight in up to 14% of patients (Level 2 evidence).
- Data on weight change with maintenance treatment are inconclusive. Low rates of weight gain (10%) are reported with bupropion, moclobemide, and nefazodone (Level 2 evidence).

4. What are the differences in discontinuation rates?

Based on a summary of metaanalyses of discontinuation rates (8,14,103–105), the range for TCA discontinuation is 19% to 31%, and the range for SSRI discontinuation is 15% to 25%. The range for differences in each of the analyses is 3% to 10%.

Conclusions About Discontinuation Rates for Antidepressants

(see Table 4.6)

- There is a modest but clinically significant difference in favour of selective serotonin reuptake inhibitors (SSRIs) over tricyclic antidepressants (TCAs) (Level 1 evidence).
- There is insufficient evidence to report on novel antidepressants compared with other agents.

5. What are the differences in potential for drug–drug interactions?

All antidepressants are metabolized by 1 or more of the cytochrome P450 (CYP) hepatic isoenzymes. Pharmacokinetic drug interactions may occur when an antidepressant or other concomitant medication also acts as an inhibitor or inducer of 1 or more of these isoenzymes (see Tables 4.3 and 4.4). Among the antidepressants, fluvoxamine is a potent CYP1A2 inhibitor, fluoxetine and fluvoxamine are potent CYP2C9 inhibitors, and fluvoxamine also inhibits CYP2C19. Fluoxetine

and paroxetine most potently inhibit CYP2D6, while nefazodone is the most potent inhibitor of CYP3A4. Protein binding is also an important variable to be taken into account; it is lower for citalopram (80%) and venlafaxine (30%) than for other SSRI and novel antidepressants.

OPTIMAL USE OF ANTIDEPRESSANTS

6. What is a rational sequential approach to managing a patient with depression beyond the first antidepressant trial?

The general principles of optimal assessment (including suicide risk) and management of depression are outlined in Section II. All antidepressants have a minimal therapeutic dose, but some patients require higher dosages for optimal effect. The SSRIs have a relatively flat dosage-response curve, based on fixed-dosage group comparisons. Nevertheless, individual patients may benefit from higher-than-usual dosing strategies. Medications like venlafaxine may have a positive dosage-response curve, with higher response rates at the higher dosage ranges (106).

Figure 4.1 (p 48S) illustrates an evidence-based algorithm summarizing treatment strategies. Studies on augmentation, combination, and switching strategies are reviewed in the context of no response (generally < 20% reduction in symptom rating scales), minimal response (20% to 50% reduction), partial response (> 50% reduction, but still symptomatic), and full response (symptom ratings within the normal range).

7. How long do you wait for a clinical response?

There should be some evidence of at least minimal or partial response after 4 weeks at a therapeutic dosage. The probability of showing a clinical response after 6 to 8 weeks of antidepressant treatment is less than 20% if there has been minimal or no response after 3 to 4 weeks (107–109). The corollary is evidence that even a minimal response (for example, 20% reduction in symptom ratings) after 2 weeks is a significant predictor of subsequent response after 6 to 8 weeks (110). Therefore, some alteration of treatment is indicated (for example, increase of dose) if there is no response after 3 to 4 weeks of antidepressant initiation. For minimal or partial responses, the clinician can continue to wait another week or so to determine whether there is continued improvement, before deciding on an alteration of strategy.

8. What do you do when a patient does not respond?

When a patient has shown only partial or no response to an optimized (usually an increased) dose of an antidepressant, the clinician should reevaluate diagnostic issues (for example, bipolarity, depressive subtype, comorbidity, or substance

Table 4.2a Frequency of side effects to cyclic antidepressants at therapeutic dosagesⁱ

Reaction	Amitriptyline	Clomipramine	Desipramine	Doxepin	Imipramine	Nortriptyline	Protriptyline	Trimipramine	Amoxapine	Maprotiline
CNS effects										
Drowsiness, sedation	✱	■	■	✱	○	■	*	✱	○	○
Insomnia	■	○	■	■	○	*	○	■ ^h	○	*
Excitement, hypomania ^a	*	*	■	*	○	■	○	*	■	■
Disorientation/confusion	○	■	—	*	■	○	—	○	■	■
Headache	■	■	*	*	○	*	—	■	■	*
Asthenia, fatigue	○	■	■	■	○	○	○	■	■	■
Anticholinergic effects										
Dry mouth	✱	✱	○	✱	✱	○	○	○	✱	✱
Blurred vision	○	○	■	○	○	■	○	■	■	○
Constipation	○	○	■	○	○	○	○	○	✱	○
Sweating	○	○	■	■	○	*	○	■	■	■
Delayed micturition ^b	■	■	—	*	○	*	*	*	○	■
Extrapyramidal effects										
Unspecified	■ ^e	* ^e	*	■ ^e	*	—	—	*	■ ^e	■
Tremor	○	○	■	■	○	○	■	○	■	○
Cardiovascular effects										
Orthostatic hypotension/dizziness	○	○	■	○	✱	■	○	○	○	■
Tachycardia, palpitations	○	○	○	■	○	■	■	■	○	■
ECG changes ^c	○ ^f	○ ^f	■ ^f	■ ^f	○ ^f	■ ^f	○ ^f	○ ^f	* ^f	* ^f
Cardiac arrhythmia	■	■	■	■	■	■	■	■	*	*
GI distress	■	○	■	*	○	*	—	*	■	■
Dermatitis, rash	■	■	■	*	■	*	*	*	○	○
Weight gain (over 6 kg)	✱	○	■	○	○	■	*	○	*	○
Sexual disturbances	■	✱	■	■	✱	*	*	*	■	*
Seizures ^d	*	* ^g	*	*	*	*	*	*	* ^g	■ ^g

* < 2%, ■ ≥ 2%, ○ ≥ 10%, ✱ ≥ 30%, — None reported in literature perused.

^aMore likely in patients with bipolar illness; ^bPrimarily in the elderly; ^cECG abnormalities usually without cardiac injury; ^dIn patients without epilepsy; ^eTardive dyskinesia reported (rarely); ^fConduction delays: increased PR, QRS or QT_c interval; ^gHigher incidence if dose above 250 mg daily clomipramine, 225 mg daily maprotiline or 300 mg daily amoxapine; ^hNo effect on REM sleep; ⁱAdapted from Bezchlibnyk-Butler and Jeffries (77).

abuse) and treatment issues (for example, adherence, and side effects), including suicide reassessment. Psychotherapy strategies can be considered at this time (see Section V).

For pharmacologic strategies, the clinician has the choice of switching, augmenting, or combining antidepressant medications. Augmentation strategies involve adding a medication

that by itself is not an antidepressant, while combination strategies involve adding a second antidepressant. Given the paucity of comparative data to inform the clinician whether to switch or augment/combine, the psychiatrist and patient must consider several factors, including the side-effect burden of a particular medication, whether there is a partial response to

Table 4.2b Frequency of side effects to selective serotonin reuptake inhibitors (SSRIs) and novel antidepressants at therapeutic dosages^s

Reaction	SSRIs					Novel agents				
	Citalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline	Nefazodone	Trazodone	Bupropion	Venlafaxine	Mirtazapine
CNS effects										
Drowsiness, sedation	○	○	○	○	○	○	✖	■	○	✖ ^f
Insomnia	○	○ ^f	○	○	○	■	■	○	○ ^f	■
Excitement, hypomania ^a	■	■	○	■	○	■	— ^k	○ ^k	○ ^k	■
Disorientation/confusion	*	○	■	*	*	○	*	■	■	■
Headache	○	○	○	○	○	○	■	○	○	■
Asthenia, fatigue	○	○	○	○	■	○	○	■	○	○
Anticholinergic effects										
Dry mouth	○	○	○	○	○	○	○	○	○	✖
Blurred vision	■	■	■	■	■	○	■ ^l	○	■	○
Constipation	■	■	○	○	■	○	■	○	○	○
Sweating	○	■	○	○	■	■	—	○	○	■
Delayed micturition ^b	■	■	■	■	*	*	*	■	*	■
Extrapyramidal effects										
Unspecified	*	■ ^g	■	■	■	*	■ ^g	■	■	*
Tremor	○	○	○	○	○	*	■	○	■	■
Cardiovascular effects										
Orthostatic hypotension/dizziness	■	○	■	○	○	○	○ ^m	■ ^o	○ ^o	■
Tachycardia, palpitations	■ ^e	* ^e	* ^e	■ ^e	■ ^e	* ^e	■	■	■	■
ECG changes ^c	*	*	*	*	*	*	■	*	*	*
Cardiac arrhythmia	*	* ^h	*	*	*	*	■ ⁿ	*	*	*
GI distress										
GI distress	○	○	✖	○	✖	○	○	○	✖	■
Dermatitis, rash										
Dermatitis, rash	*	■	■	*	■	*	*	■	■	*
Weight gain (over 6 kg)										
Weight gain (over 6 kg)	* ⁱ	* ⁱ	*	■ ⁱ	* ⁱ	—	■	* ⁱ	* ⁱ	✖
Sexual disturbances										
Sexual disturbances	■	✖ ^j	✖	✖ ^j	✖ ^j	*	* ^j	* ^{p,j}	✖ ^j	*
Seizures^d										
Seizures ^d	*	*	*	*	*	*	*	* ^q	*	*

* < 2%, ■ ≥ 2%, ○ ≥ 10%, ✖ ≥ 30%, — None reported in literature perused.

^aMore likely in patients with bipolar illness; ^bPrimarily in the elderly; ^cECG abnormalities usually without cardiac injury; ^dIn patients without epilepsy; risk increased with elevated plasma levels; ^eDecreased heart rate reported; ^fEspecially if given in the evening; ^gTardive dyskinesia reported (rarely); ^hSlowing of sinus node and atrial dysrhythmia; ⁱWeight loss reported initially; ^jPriapism reported; ^kLess likely to precipitate mania; ^lFound to lower intraocular pressure; ^mLess frequent if drugs given after meals; ⁿPatients with preexisting cardiac disease have a 10% incidence of premature ventricular contractions; ^oHypertension reported; ^pImproved sexual functioning; ^qHigher incidence if doses used above 450 mg daily of bupropion or in patients with bulimia; ^sSedation decreased at higher doses (above 15 mg); ^tAdapted from Bezchlibnyk-Butler and Jeffries (77).

the index antidepressant, potential side effects of new treatments, and previous medication history.

9. How effective are switching strategies?

Antidepressants can be switched either within the same medication class (or neurochemical action) or to a different class (or neurochemical action). Switching within the class is a poor choice with the TCAs, but can be an effective strategy for SSRIs. The response rate when switching to another SSRI is generally better when the first SSRI is poorly tolerated (66%) than when the patient is refractory (48%) (111). Expert

clinicians would generally switch patients who have not responded to an optimized and tolerated dose of the first drug to a medication in a different class—for example, from an SSRI to a serotonin norepinephrine reuptake inhibitor (SNRI), a serotonin antagonist and reuptake inhibitor (SARI), a noradrenaline and dopamine modulator (NDM) or a noradrenaline reuptake inhibitor (NRI).

When considering a switch to another antidepressant, drug–drug interactions must be considered in choosing a starting dosage. For example, a switch from fluoxetine, a long half-life SSRI that significantly inhibits CYP2D6, to a TCA that requires this isoenzyme for metabolism (for example,

Table 4.2c. Frequency of side effects to monamine oxidase inhibitors and reversible inhibitor of MAO-A antidepressants at therapeutic dosages^k

Reaction	Isocarboxazid ^j	Phenelzine	Tranylcypromine	Moclobemide
CNS effects				
Drowsiness, sedation	■	○	○	■
Insomnia	■ ^e	○ ^e	○ ^e	○ ^e
Excitement, hypomania ^a	■	○	○	○
Disorientation/confusion	■	■	■	■
Headache	○	■	—	○
Asthenia, fatigue	■	*	*	*
Anticholinergic effects				
Dry mouth	○	✱	○	○
Blurred vision	■	○	■	○
Constipation	■	○	■	■
Sweating	*	■	—	■
Delayed micturition ^b	■	■	■	*
Extrapyramidal effects				
Unspecified	■	○	*	*
Tremor	○	○	■	■
Cardiovascular effects				
Orthostatic hypotension/dizziness	○	○	○	○
Tachycardia, palpitations	—	○ ^f	○ ^f	■
ECG changes ^c	■	* ^g	* ^g	■
Cardiac arrhythmia	■	*	*	■
GI distress				
	○	○	■	○
Dermatitis, rash				
	■	*	■	■
Weight gain (over 6 kg)				
	■	○	■	*
Sexual disturbances				
	■	✱ ^h	■ ^h	*
Seizures^d				
	—	*	— ⁱ	*

* < 2%, ■ ≥ 2%, ○ ≥ 10%, ✱ ≥ 30%, — None reported in literature perused.

^aMore likely in patients with bipolar illness; ^bPrimarily in the elderly; ^cECG abnormalities usually without cardiac injury; ^dIn patients without epilepsy; ^eEspecially if given in the evening; ^fDecreased heart rate reported; ^gShortened QTc interval; ^hPriapism reported;

ⁱMay have anticonvulsant activity; ^jNot currently available in Canada; ^kAdapted from Bezchlibnyk-Butler and Jeffries (77).

desipramine) indicates that lower-than-usual starting dosages of the TCA should be used. This is also a situation where plasma TCA monitoring would be appropriate.

Generally, there is no need to stop one antidepressant for a time before starting another. With most drugs, the first antidepressant can be tapered while starting another, but patients may experience additive side effects in the overlap period. For a patient who has not tolerated the first antidepressant, it may be wise to provide a washout period, allowing the side effects to dissipate before starting a second antidepressant. Classic MAOIs require a 2-week medication washout prior to starting another antidepressant, while a 3-day washout for moclobemide is recommended (see Table 4.5).

10. How effective are augmentation strategies?

Augmentation strategies are among the best validated pharmacologic treatments for refractory depressive disorders. There are, however, significant limitations to our knowledge,

because most of the studies involve small sample sizes and report augmentation of TCAs more often than SSRIs or other agents. There are also few placebo-controlled trials of augmentation strategies, and there are even fewer direct comparisons of different augmentation strategies.

Lithium augmentation has the most evidence supporting its use. Two metaanalyses have shown that lithium augmentation is effective in about 60% of refractory patients (112,113). Lithium should be given at dosages of greater than 750 mg daily, or at a dosage that achieves serum levels of at least 0.5 meq/L. A suggested dosage schedule is 600 mg daily for 1 week, increasing to 900 mg daily for 1 week, and then titrating to adequate serum levels for another week. If there is no response after 3 to 4 weeks, then alternate strategies can be used. Lithium augmentation is associated with the usual side effects of lithium use.

Triiodothyronine (T₃, liothyronine) has also been shown to be effective in placebo-controlled RCTs. One RCT found comparable efficacy between T₃ and lithium, both of

which were superior to placebo (114). T₃ also appears to be more effective than thyroxine (T₄) (115). A metaanalysis, however, showed equivocal results, due to the influence of a single larger negative study (116). T₃ is usually started at a dose of 25 mcg daily and increased to 50 mcg after 1 week, if necessary. With no response at the higher dose for 2 weeks, another strategy should be used. T₃ is generally well tolerated.

Both lithium and T₃ studies have primarily involved patients who were refractory to monotherapy with TCAs or MAOIs. Only 2 studies examined lithium augmentation in SSRI nonresponders (with citalopram [117] and fluoxetine [118]). There is only limited evidence to date to support lithium or T₃ augmentation of the novel-action antidepressants.

Other strategies have focused on SSRI nonresponders. Buspirone, a partial postsynaptic 5-HT_{1A} agonist with catecholamine effects, was beneficial in a number of open-label studies, but a placebo-controlled RCT was negative, likely

Table 4.3 Degree of CYP inhibition by SSRIs and novel antidepressants at usually effective dosages

Drug	CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4
Citalopram	Mild	None	Mild	Mild	None
Fluoxetine	Mild	Mild	Mild	Significant	Mild
Fluvoxamine	Significant	Mild	Moderate	Mild	Moderate
Paroxetine	Mild	Mild	Mild	Significant	Mild
Sertraline	Mild	Mild	Mild	Mild	Mild
Bupropion	None	None	None	Moderate	None
Moclobemide	Mild	None	Mild	Mild	None
Nefazodone	Mild	None	None	Mild	Significant
Reboxetine	None	None	None	Mild	Mild
Venlafaxine	None	None	None	Mild	None
Mirtazapine	None	None	None	Mild	None

Modified from: Preskorn, SH. Antidepressant options in primary care. Clinical cornerstone - Depression 1999;1:1–16 and Kent, JM. SNaRIs, NaSSAs, and NaRIs: new agents for the treatment of depression. Lancet 2000;355:911–8.

Mild 20%–50%, Moderate > 50%–150%, Significant > 150%

Table 4.4 Clinically significant substrates for antidepressant-inhibited isoenzymes

The following table provides information on potential drug interactions between frequently prescribed antidepressants and other medications. Less concern when > 20% renal drug clearance. Less concern when > 1 isoenzyme involved in metabolic degradation. More concern when concomitant drug has significant dose-related side effects or narrow therapeutic-to-toxic range. Metabolites may inhibit different isoenzymes or be substrates for different isoenzymes than the parent compound.						
Antidepressant	Isoenzyme inhibited	Drugs whose blood levels may be elevated if used concomitantly with the specified antidepressant				
Bupropion	2B6	Cyclophosphamide	Ifosfamide	Orphenadrine		
Citalopram	1A2, 2D6, 2C19 (weak)	None known or predicted to be clinically important.				
Fluoxetine	2D6 2C9	Alprazolam ^b Amitriptyline ^b Astemizole ^a	Desipramine ^{b,d}	Flecainide ^a	Midazolam ^b Nortriptyline ^{b,d} Perphenazine ^c Phenytoin ^d Pindolol ^c Propafenone ^a Propranolol ^c Risperidone ^c	Terfenadine ^a Thioridazine ^c Timolol ^c Trazadone ^b Triazolam ^b S-warfarin ^d (active)
(Norfluoxetine)	(2D6) (3A3/4)	Carbamazepine ^d Cisapride ^a	Diazepam ^c Doxepin ^b	Haloperidol ^c Imipramine ^b Labetalol ^c Metoprolol ^c Mexiletine ^a		
Fluvoxamine	1A2 3A3/4	Alprazolam ^b Amitriptyline ^c Carbamazepine ^d Cisapride ^a Clomipramine ^c Clozapine ^c	Desipramine ^c	Haloperidol ^c Imipramine ^c Midazolam ^b		Theophylline ^d Triazolam ^b S-warfarin ^d (active)
Mirtazapine	1A2	None known or predicted to be clinically important				
Moclobemide	None	None known or predicted to be clinically important				
Nefazodone	3A3/4	Alprazolam ^b Astemizole ^a Carbamazepine ^d Cisapride ^a			Midazolam ^b	
Paroxetine	2D6	Amitriptyline ^b Desipramine ^b	Doxepin ^b Flecainide ^a	Haloperidol ^c Imipramine ^b Labetalol ^c Metoprolol ^c Mexiletine ^a	Nortriptyline ^a Perphenazine ^c Pindolol ^c Propafenone ^a Propranolol ^c	Thioridazine ^c Timolol ^c Trazadone ^b
Sertraline	1A2, 2C9, 2C19, 2D6, 3A4					
Venlafaxine	2D6 (weak)	None known or predicted to be clinically important				

^aAvoid; ^bReduce dose of substrate; ^cMonitor for side effects; ^dMeasure drug plasma levels.

No notation—no information to indicate interaction is of clinical significance. Adapted from Michalets, EL. Update: clinically significant cytochrome P450 drug interactions. Pharmacotherapy 1998;18:84–112.

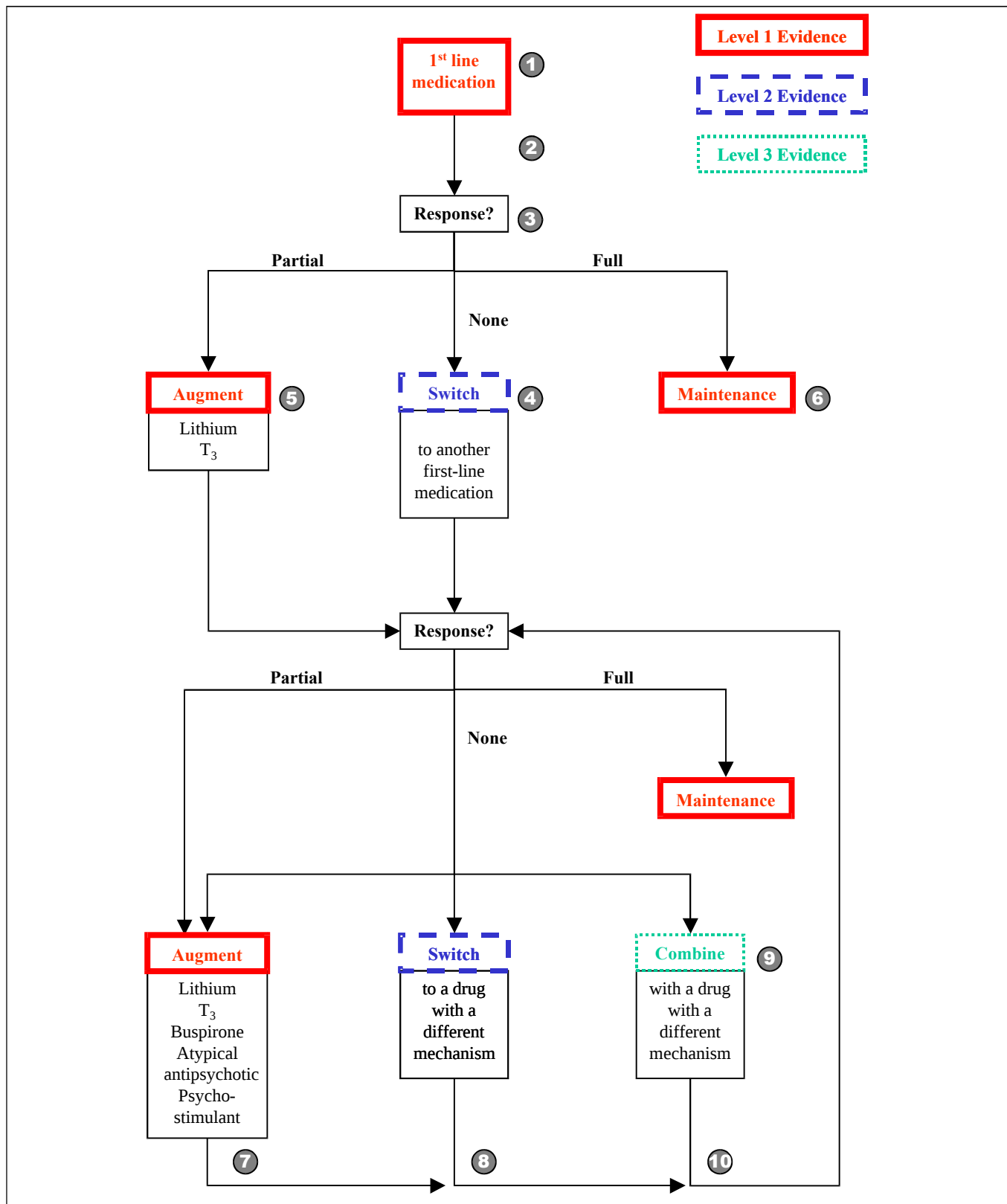


Figure 4.1 Evidence-based algorithm for treatment of refractory major depression. Note that treatment may not be sequential—any step of the algorithm can be bypassed depending on the clinical state of the patient.

Notes to Figure 4.1 Evidence-based algorithm for treatment of refractory major depression

1. First-line medication is chosen based on clinical factors such as previous response, depressive subtype, comorbidity, side effects, and potential for drug–drug interactions. Doses should be increased every 2 to 4 weeks as necessary to achieve optimal response.

2. At each decision point, when there is partial or no response, the clinician should

- Reevaluate diagnostic issues (for example, subtype, comorbidity, bipolarity, substance abuse)
- Reassess suicide risk
- Consider adding psychotherapy (see Section V)
- Consider electroconvulsive therapy (ECT) (especially if high suicide risk, severe or chronic illness, psychotic features, physical deterioration, or pregnancy).

3. Definitions of response have usually used scores from standardized rating scales like the Hamilton Depression Rating Scale (HDRS). Generally, minimal improvement is defined as less than 20% reduction in HDRS scores compared with baseline; partial remission as 20% to 50% reduction in HDRS score, or greater than 50% reduction in HDRS but residual score still outside the normal range; remission as a score within the normal range. Busy clinicians may be more likely to use global rating scales like the Clinical Global Impression Improvement Scale—very much improved (remission), much improved or minimally improved (partial remission), not improved or worse (no response).

4. Switching to another antidepressant with a different neurochemical action is generally recommended if there is no response after optimizing the first antidepressant. Switching from one selective serotonin reuptake inhibitor (SSRI) to another can be considered, but response rates are higher in patients who are SSRI-intolerant rather than nonresponsive.

5. Many experts hold off augmentation until after the second antidepressant; however, there is some opinion that augmentation can be tried if there is a partial response with the first medication. In this situation, only validated augmentation strategies with Level 1 evidence (lithium, T₃) should be considered. Note that lithium and T₃ augmentation has only been studied with tricyclic antidepressant (TCAs) and SSRIs.

Factors to consider in deciding between augmentation and switching after the first antidepressant:

- Augmentation strategies using lithium and T₃ are the best validated treatments.
- Side effects of augmentation, especially with lithium, are generally greater than with antidepressant monotherapy.
- Benefits of augmentation include building on a partial response, rapid onset of effect, allowing a longer time on the initial antidepressant, maintaining therapeutic optimism with patients.
- Benefits of switching to another monotherapy include: simpler treatment, fewer side effects, no concerns about drug–drug interactions, better compliance.

6. Maintenance medications should be continued at the same dose for at least 6 months. Longer-term maintenance (at least 2 years) should be used for frequent episodes (2 or more in 5 years), recurrent episodes (3 or more, lifetime), chronic episodes, severe episodes (for example, with psychotic symptoms or marked suicidal ideation), difficult-to-treat episodes, and in older-age patients.

7. After an unsuccessful augmentation, consider combining another antidepressant for partial or no response.

8. After 2 second-generation antidepressants with different neurochemical actions have been tried, consider a TCA (nortriptyline or desipramine) with therapeutic drug monitoring (serum levels), or a monoamine oxidase inhibitor (MAOI).

9. There is now considerable theoretical rationale to combine antidepressants with different neurochemical actions for monotherapy nonresponders. However, there is as yet only limited evidence to support combination antidepressant treatment. Only open-label case series (Level 3 evidence) are available. This limited evidence suggests that SSRI plus desipramine, SSRI plus moclobemide, SSRI plus bupropion, bupropion plus venlafaxine, TCA plus venlafaxine, mirtazapine combinations, and the older TCA plus MAOI combination may be beneficial for refractory depression. Limitations of combination antidepressants include increased side effects, potential drug–drug interactions, higher cost, and the possibility of response to monotherapy with the new antidepressant.

10. Adding augmentation to combination antidepressants can be considered for the most refractory patients.

because of a high placebo response rate (54%) (119). There has been much interest in pindolol, a beta-blocking drug that, in low doses, acts as a specific antagonist of the 5-HT_{1A} pre-synaptic autoreceptor. A large RCT of pindolol to augment SSRIs and clomipramine in refractory depression was negative, however, with pindolol and placebo having identical response rates of approximately 13% (120). Finally, a small RCT in patients with nonpsychotic depression refractory to fluoxetine showed that addition of olanzapine was more effective than either drug alone (121).

11. How effective are combination antidepressant strategies?

While the use of combination antidepressant therapy is common in clinical practice (122), there are few RCTs to support this strategy in treating refractory depression. Combined MAOI and TCA therapy was not superior to treatment with either agent alone (123), nor was the combination of desipramine and fluoxetine superior to either high-dose fluoxetine alone or lithium augmentation of fluoxetine (124). Open studies of combination antidepressant medications have been described for an SSRI plus moclobemide, an SSRI plus bupropion, bupropion plus venlafaxine, and a TCA plus venlafaxine, as well as for mirtazapine combinations. The rationale for combining medications, however, is more sound now that there are antidepressants with very different neurochemical actions. Preliminary studies suggest that combining fluoxetine with desipramine is effective for refractory depression but must be used with caution (125). Other open-label studies have suggested that various combination antidepressant treatments are beneficial when there has not been response to a single antidepressant, but no controlled studies are yet available. More research on combination antidepressant treatment is urgently needed.

12. What are the relative benefits of switching versus augmentation/combination?

Advantages of switching to another antidepressant, compared with augmentation/combination strategies, include the simplicity of monotherapy and the lack of potential drug–drug interactions. Monotherapy may also, but not necessarily, have fewer side effects and better adherence. Potential advantages of augmentation, compared with switching, include maintenance of therapeutic optimism (not “giving up” on a drug), avoidance of potential discontinuation symptoms, and the possibility of rapid response for some augmentation agents. Adding another agent also “buys more time” on the initial medication and may build on partial responses.

The benefits of combining antidepressants include the possible benefits of using multiple neurochemical actions, building on a partial response, and using lower doses of each agent, compared with monotherapy. The drawbacks of combination antidepressant use include the possibility that the patient

might simply respond to monotherapy with the second agent, the risk of additive side effects and poorer compliance, and the cost of using multiple medications.

Recommendations for Managing Nonresponse to an Antidepressant	
(see Table 4.6)	
Once an antidepressant is selected, an initial improvement (at least 20% reduction in depression scores) should be seen within 3 to 4 weeks. Otherwise, the following interventions are indicated:	
First-line treatments	Optimize the antidepressant by increasing the dose as tolerated (Level 2 evidence).
Second-line treatments	- Switch to an antidepressant with a different neurochemical action (Level 2 evidence). - Augment with lithium or triiodothyronine (T₃) (Level 1 evidence).
Third-line treatments	- Switch to an antidepressant with a similar neurochemical action (Level 2 evidence). - Augment with buspirone or an atypical antipsychotic such as olanzapine (Level 2 evidence). - Combine with another antidepressant (Level 3 evidence).
Not recommended	Augment with pindolol (Level 2 evidence).

MAINTENANCE THERAPIES

13. How long do you keep patients on an antidepressant once they are better?

Prevention of relapse and recurrence is important because depression is regarded as a chronic and/or recurrent illness. Previous attention focused on phases of treatment, with an acute phase lasting 8 to 12 weeks, a continuation phase of treatment lasting 4 to 6 months, and a maintenance phase lasting 6 months to lifetime (126). In part, this was based on the idea that the average duration for an untreated depressive episode is approximately 6 months. Return of symptoms during this period was seen as relapse of the same episode, whereas return of symptoms later indicated a new episode, or recurrence. The objectives of treatment differ among phases: for the acute phase, suppression of symptoms; for the continuation phase, prevention of relapse; and for the maintenance phase, prevention of recurrence.

In clinical practice, however, it is often difficult or impossible to determine whether a return of symptoms is a relapse or a recurrence. A recent metaanalysis of continuation and maintenance studies indicates that the period of continuation or maintenance therapy does not seem to influence the relapse rate once medications are discontinued (127). A single concept of maintenance treatment—how long a patient should stay on an antidepressant once the patient is better—is simpler and more relevant to the clinical situation.

Recommendations for the duration of antidepressant therapy have generally been extended during the past decade, and this important aspect of depression management continues to be influenced by new data. For patients with a single episode of depression, the risk of relapse is higher in the first 6 months from the time of full remission of symptoms. After that time, the difference in relapse rates between an active antidepressant and a placebo may not be significant (128). Therefore, all patients should stay on antidepressants for a minimum of 9 months (8 to 12 weeks or more of active treatment leading to full remission, followed by 6 months of maintenance treatment). Patients with risk factors need longer maintenance treatment (see below). The dosage of the antidepressant in the maintenance phase should be the same as in the acute phase.

There are few data on the duration of maintenance treatment for augmentation or combination strategies. After successful lithium augmentation, patients should be kept on lithium and antidepressants for 6 months or longer (129).

14. Who should be maintained longer on an antidepressant?

Unfortunately, there are no consistent, evidence-based biological markers that predict recurrence. Different demographic and clinical parameters have been identified as risk factors for relapse and recurrence. Patients with the following risk factors should be maintained on medications for a minimum of 2 years: older age, chronic episodes, severe or life-threatening episodes, psychotic episodes, difficult-to-treat episodes, recurrent episodes (3 or more, lifetime), and frequent episodes (2 or more episodes in 5 years) (127). At the end of the recommended period, there should be a collaborative reassessment by the patient and physician about continuing maintenance medication. The decision needs to balance the benefits (that is, preventing recurrence) and the risks (for example, side effects, cost, and inconvenience) of staying on medications against the option of discontinuing medication and monitoring for recurrence. If the antidepressant is discontinued, it should be gradually tapered to avoid discontinuation symptoms (130,131).

Recommendations for Maintenance Pharmacotherapy

(see Table 4.6)

- All patients should be maintained on antidepressants for at least 6 months after clinical remission (Level 1 evidence).
- Patients with the following risk factors should be maintained on antidepressants for at least 2 years: older age, psychotic features, chronic episodes, recurrent episodes (3 or more lifetime), frequent episodes (2 or more in 5 years), difficult-to-treat episodes, and severe episodes (Level 2 evidence).
- The antidepressant dosage in the maintenance phase should be the same as in the acute phase (Level 2 evidence).
- Antidepressants should be tapered slowly to avoid discontinuation symptoms (Level 3 evidence).

OTHER BIOLOGICAL TREATMENTS FOR DEPRESSIVE DISORDERS

Electroconvulsive Therapy

15. How effective is electroconvulsive therapy (ECT) for depressive disorders?

ECT is generally accepted to be the most rapid and effective treatment available for severe major depressive episodes (MDEs). ECT is associated with a 60% to 80% remission rate, with maximum response typically attained after 2 to 4 weeks. There are few data, however, comparing ECT with SSRIs and newer antidepressant medications (132).

ECT is predominantly used to treat refractory depression but should be considered as a first-line treatment in acutely suicidal or severely medically compromised patients, including pregnant women. Some controlled studies suggest that patients who are refractory to antidepressants have a lower response rate to ECT (133,134) or higher relapse rates within 6 months (135,136), but naturalistic studies did not show a relation between antidepressant refractoriness and clinical outcome (137).

16. What are the recommended treatment parameters for ECT?

During the acute-treatment phase, ECT should be carried out 2 to 3 times weekly, for up to 6 weeks. The less frequent schedule may minimize some of the immediate cognitive side effects of ECT, but the onset of response is slower (138). Recent research has shown that it is important, especially with unilateral electrode placement, to optimize the electrical dose relative to the seizure threshold of each patient at the first treatment. Individual assessment of seizure threshold is critical because there is at least a 12-fold range in seizure threshold among patients with depression who are receiving ECT (139).

Compared with bilateral electrode placement, unilateral placement at a suprathreshold dose produces fewer immediate and persistent cognitive side effects, without compromising treatment efficacy. An electrical dose of 3 to 6 times the seizure threshold is required for unilateral electrode placement to have the same efficacy as bilateral ECT (140). It is important that ECT equipment be adequately powered to deliver these suprathreshold doses (141). Duration of the seizure is a less important marker of efficacy than electroencephalogram (EEG) evidence of high seizure intensity (142).

Although ECT is usually conducted on inpatients, outpatient ECT practice is growing, largely because of its use for maintenance treatment. Ambulatory ECT may be administered on an outpatient basis for a carefully selected population of patients in a facility that is properly equipped to do so, according to practice guidelines (143).

Table 4.5 Washout recommendations for switching antidepressants

Switching from	Switching to				
	SSRI	Novel (mixed action)	TCA	RIMA	MAOI
SSRI Citalopram Fluoxetine Fluvoxamine Paroxetine Sertraline	No washout Be aware of additive serotonergic effects for up to 1 week after stopping SSRI (5 weeks for fluoxetine)	No washout Be aware of additive serotonergic effects for up to 1 week after stopping SSRI (5 weeks for fluoxetine)	No washout Be aware that SSRIs can increase serum TCA levels for up to 1 week after stopping SSRI (5 weeks for fluoxetine)	1 week (5 weeks for fluoxetine) Some data indicate that an SSRI and RIMA can be safely combined, but this requires specialist input.	1 week (5 weeks for fluoxetine)
Novel (mixed action) antidepressants Bupropion SR Mirtazapine Nefazodone Trazodone Venlafaxine Venlafaxine XR	No washout	No washout Venlafaxine should be started at a lower dose to avoid additive noradrenergic effects Bupropion should be started at a lower dose to avoid additive noradrenergic effects	No Washout TCA should be started at a lower dose to avoid additive noradrenergic effects	3–5 days No Washout with bupropion	1 week
TCA Amitriptyline Desipramine Imipramine Nortriptyline and others	No washout Be aware that SSRI can increase serum levels of TCAs for up to 1 week after stopping TCA. Be aware of additive serotonergic effects when switching from clomipramine to SSRIs.	No washout Venlafaxine should be started at a lower dose to avoid additive noradrenergic effects Bupropion should be started at a lower dose to avoid additive noradrenergic effects	No washout	No washout	1 week
RIMA Moclobemide	3 days	3 days	3 days	Not applicable	3 days
MAOI Phenelzine Tranylcypromine	2 weeks	2 weeks	2 weeks	2 weeks	2 weeks

SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; RIMA = reversible inhibitor of MAO-A; MAOI = monoamine oxidase inhibitor.

17. What are the adverse effects associated with ECT?

ECT is a safe procedure, and mortality and morbidity rates for ECT are extremely low in the modern era. Apart from raised intracranial pressure, there are no absolute contraindications to ECT. Careful preanesthetic examination is essential, particularly for patients at higher risk, including those with myocardial ischemia, cardiac arrhythmias or pacemakers, or abdominal aneurysm. Mortality associated with ECT is estimated to be 0.2 deaths per 100 000 treatments and is most likely related to cardiovascular complications (144). The adverse-event rate after ECT is around 0.4%. Adverse events can include musculoskeletal injuries, dental damage, oral lacerations, and persistent myalgia (132). Nausea, headaches, and muscle aches post-ECT are common but can be treated with antiemetics and analgesics, if necessary.

The cognitive side effects associated with ECT are well documented. Objective memory testing shows a transient retrograde amnesia that lessens with time, so that no cognitive deficits are apparent at 6 months post-ECT, although there may be persistent spotty memory gaps for events occurring around the time of the ECT. Subjective memory complaints include immediate, and some persistent (at least 2 months), deficits in some autobiographical memory, mostly with impersonal memories (for example, public events) rather than with personal memories (145).

Greater cognitive side effects are generally associated with use of bilateral electrode placement; electrical dosages at

higher suprathreshold levels; treatment 3 times weekly, compared with twice weekly; and persistent depressive mood state. Continuation and maintenance ECT treatment is less likely to cause cognitive side effects, possibly due to the longer time interval between treatments (146). There is no credible evidence that ECT causes any form of structural brain damage (147). Prospective neuroimaging studies with CT and MRI show no brain structural changes after ECT.

18. Should ECT be combined with antidepressant medication?

There is little evidence that combining antidepressants with ECT improves the response, especially with prospective studies (148,149). Patients undergoing ECT have usually failed antidepressant treatment, so there is little rationale to continue the same medication. Starting a new medication causes clinical confusion when patients respond and in determining adverse effects. There is no evidence that starting a medication with ECT has any effect on relapse rates, compared with starting a medication following the last ECT session.

There has been a suggestion that lithium is associated with delirium or prolonged confusion after ECT, but this requires further investigation. The use of sedatives, such as benzodiazepines, and anticonvulsants, such as carbamazepine and valproic acid, may inhibit seizures or shorten seizure

duration; therefore, their use with ECT should be minimized (143,146).

19. How can you prevent relapse after ECT? How effective is maintenance ECT?

The relapse rate without maintenance treatment following ECT is high: between 50% and 95% of patients relapse within 6 months. Predictors of relapse include pre-ECT medication resistance and greater severity of depression. Maintenance medication treatment for at least 1 to 2 years is nearly always indicated to prevent relapse. Lithium and antidepressants can reduce the relapse rate. Medications that were used optimally and failed prior to ECT should not be used for post-ECT maintenance.

ECT itself may also be used for maintenance treatment, with treatment schedules ranging from once weekly to once monthly (132,135). There is, however, a lack of controlled and well-defined outcome studies; evidence is limited to case series and reports. Suggested indications for use of maintenance ECT are as follows: a history of responsiveness to ECT in recurrent episodes; refractoriness to, or intolerance of, prophylactic pharmacotherapy; highly recurrent and easily relapsing symptoms; psychotic symptoms; and patient preference (146).

Recommendations for Electroconvulsive Therapy

(see Table 4.6)

- Electroconvulsive therapy (ECT) is an effective treatment for major depressive disorder (MDD) (Level 1 evidence).
- Indications for ECT include acute suicidal risk, severe physical deterioration, psychotic features, refractoriness to medications, and patient preference.
- Unilateral electrode placement requires suprathreshold doses of ECT (Level 2 evidence).
- Side effects of ECT are generally mild, with evidence for a transient, short-term memory disturbance (Level 2 evidence).

Light Therapy

20. How effective is light therapy in treating depressive disorders?

The efficacy of light therapy for seasonal mood disorders has been established by several large-sample RCTs comparing light therapy to plausible placebos (150,151), metaanalyses (152), and published clinical guidelines (43). The response rate for light therapy is 60% to 90%, with response occurring within 2 to 3 weeks.

The efficacy of light therapy for nonseasonal depressive disorders is more controversial. The controlled studies have small samples, short treatment durations (1 to 4 weeks), and equivocal results; thus, there is currently insufficient evidence to recommend light therapy for nonseasonal depression. Its use as an adjunctive treatment with medications may, however, be considered for some patients (153).

21. What are the recommended treatment parameters for light therapy?

The fluorescent light box is the gold standard light device, because there are not yet adequate efficacy data for head-mounted devices and dawn simulators (43). The recommended treatment regimen is 10 000 lux intensity for 30 minutes daily in the early morning, as soon as possible after awakening. The light box should have an ultraviolet filter to screen out harmful ultraviolet rays. Response to light therapy generally occurs within 2 to 4 days, and measurable improvement is often seen in 1 week, but some responses may occur over 2 to 4 weeks.

Side effects of light therapy, including eyestrain, visual disturbances, headache, agitation or feeling "wired," nausea, sweating, and sedation, are generally mild and subside with time or with a reduced dose of light. Light therapy can precipitate hypomania or mania in susceptible patients. There is no evidence of ocular damage with proper use of light therapy. Nevertheless, ophthalmological assessment and monitoring are recommended if patients have ocular risk factors for potential light toxicity, including preexisting retinal disease; systemic illnesses that affect the retina (for example, diabetes); use of photosensitizing medications such as phenothiazine antipsychotics, lithium, melatonin, or St John's wort; and the elderly.

Most patients (but not all) experience rapid recurrence of symptoms after discontinuation of light therapy. Therefore, patients should continue using light therapy throughout their period of risk for winter depression and, usually, discontinue treatment during the asymptomatic summer months. There are few data on long-term or maintenance use of light therapy for SAD or nonseasonal depression.

Recommendations for Light Therapy

(see Table 4.6)

- Light therapy is an effective treatment for recurrent major depressive disorder (MDD) with a seasonal pattern, of mild-to-moderate severity (Level 1 evidence).
- An adequate trial of light therapy should be 2 to 4 weeks of 10 000 lux fluorescent light for 30 minutes daily, in the early morning (Level 2 evidence).
- Patients usually need to continue daily light therapy throughout the winter and can discontinue treatment in the summer (Level 3 evidence).
- There is insufficient evidence regarding the efficacy of light therapy for long-term or maintenance use.

22. How effective are other biological treatments for depressive disorders?

St John's Wort

Several metaanalyses have summarized RCTs showing that extracts of *Hypericum perforatum*, also known as the plant St John's wort, are more effective than placebo and equivalent

to low-dose antidepressants for the short-term treatment of mild-to-moderate depression (154). The dosages of *Hypericum perforatum* used in the RCTs ranged from 300 to 900 mg daily. Side effects of *Hypericum perforatum* appear to be milder and less frequent than those experienced with standard antidepressants. These metaanalyses, however, also highlighted serious methodological limitations in all the previous RCTs (154,155). A large placebo-controlled RCT that addressed these limitations found that St John's wort was not effective for treatment of moderately severe MDD (121).

Some cautions for the use of *Hypericum perforatum* should be noted. There is no regulation of dosage or quality of *Hypericum perforatum* preparations in Canada or the US. The mechanism of action is unknown, but serotonergic and dopaminergic effects have been described. There is no evidence that it is an MAOI. *Hypericum perforatum* is associated with adverse effects, including photosensitivity, and there are studies showing that it has important pharmacokinetic interactions with disparate agents, including immunoregulatory compounds, anticoagulants, and anti-infective agents. Drug-induced hypomania and the serotonin syndrome have been reported. Therefore, combining *Hypericum perforatum* with other medications, including antidepressants, should be done only with caution.

Sleep Deprivation

Many studies have shown that total sleep deprivation, where patients are kept awake for up to 40 hours, can temporarily improve depressive symptoms, sometimes with dramatic results (156–158). The antidepressant effect is usually transient in that most patients relapse after even a brief recovery sleep; however, up to 15% of patients in clinical studies can have sustained responses following total sleep deprivation. Efforts to prevent the rapid relapse after total sleep deprivation have included use of modified partial sleep-deprivation protocols, especially with sleep deprivation in the second half of the night (for example, sleeping from 10:00 pm to 2:00 am). Even partial sleep deprivation, however, is difficult for patients to continue for more than a week. Other strategies to sustain the antidepressant effect include combining sleep deprivation with antidepressant medications, lithium, pindolol, and bright-light treatment. Placebo-controlled studies are obviously difficult to conduct for such a treatment, but several controlled studies of sleep deprivation support these combined treatments.

Given the rather simple procedure, sleep deprivation can be considered an adjunctive treatment to medications, particularly when a rapid response is required (for example, in acutely suicidal inpatients). One protocol supported in the literature includes 3 total sleep-deprivation periods within 1 week (159). During each 48-hour period, the patient is awake from 7 am on day 1 to 7 pm on day 2 (36 hours of sleep deprivation). This is followed by recovery sleep from 7 pm to 7 am on day 3 (12 hours sleep). The next sleep deprivation period then begins anew.

Table 4.6 Criteria for levels of evidence and lines of treatment recommendations

Level of evidence	Criteria
1	Metaanalysis or replicated randomized controlled trial (RCT) that includes a placebo condition
2	At least 1 RCT with placebo or active comparison condition
3	Uncontrolled trial with 10 or more subjects
4	Anecdotal case reports
Line of Treatment	Criteria
First-line	Level 1 or Level 2 evidence plus clinical support
Second-line	Level 3 evidence or higher ^a plus clinical support
Third-line	Level 4 evidence or higher ^a plus clinical support
Not recommended	Level 1 or Level 2 evidence for lack of efficacy

^aTreatments with higher levels of evidence may be listed as lower lines of treatment due to clinical issues such as side effect or safety profile.

Exercise

A metaanalysis concluded that the few studies available have methodological shortcomings and that conclusions about effectiveness could not be made (160). One RCT, however, for elders with depression, found that exercise was as effective as sertraline and the combination after 16 weeks but that the sertraline sample had a faster onset of response (161). In a 6-month follow-up to this study, the exercise sample had a lower relapse rate than did the medication sample (162). Including exercise in a treatment program, when appropriate, may have several advantages in terms of cost and side-effect profile, and it may therefore be potentially useful as a preventative strategy.

Surgical Treatments

Modern psychosurgery, also called limbic surgery, consists of stereotactic neurosurgery that places small, selective lesions in the brain. Modern limbic surgery programs have strict criteria and guidelines to identify appropriate patients that have been refractory to medications and ECT and to follow results of treatment. The procedures currently used are anterior cingulotomy or capsulotomy (163) and subcaudate tractotomy (164). There are no controlled studies of limbic surgery, but large open series involving the most treatment-refractory patients have shown that 34% to 62% of patients have good or very good improvement with these limbic surgeries. Mortality and morbidity rates are very low. No significant behavioural or intellectual deficits, and no changes in personality, have been reported for the procedures. Psychosurgery can be considered for patients with the most intractable illnesses who are suicidal or chronically severely impaired due to depression.

Vagus Nerve Stimulation

Vagus nerve stimulation (VNS) is an approved treatment for drug-refractory epilepsy that is being investigated for refractory MDD. An electrical wire is surgically implanted in the vagus nerve in the neck and connected to a stimulator located

in the chest wall (165). In an open trial, intermittent stimulation of the vagus nerve resulted in a 40% response rate in treatment-resistant patients (166). Controlled studies are now in progress.

Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) involves the stimulation of cortical neurons by magnetic induction, using a brief, high-intensity magnetic field. The electrical current is rapidly turned on and off to produce a time-varying magnetic field lasting for about 100 to 200 microseconds. For treatment, repetitive stimulation with frequencies in the range of 1 to 20 Hz is conducted over the course of about 30 minutes. The use of a hand-held wand over the scalp results in neuronal stimulation and depolarization to a depth of about 2 cm below the brain's surface. Although primarily used as a diagnostic tool for neurological examination, preliminary studies suggest that TMS can exert short-term antidepressant effects (167).

TMS is an attractive potential treatment because it can be conducted in outpatient settings, does not require anesthesia or sedation, has no effects on cognition, and has minimal side effects, such as mild headache and discomfort at the site of stimulation. Recent sham-controlled, short-duration studies have shown effects comparable with antidepressant medications (165). Potential clinical uses include the treatment of medication-refractory patients (perhaps in place of ECT) or, because of its rapid onset of effect, to hasten clinical response in conjunction with antidepressants. There is still, however, no clinical consensus about the optimal parameters of treatment, including frequency and anatomic location of stimulation. Most of the positive results have not yet been replicated, the follow-up periods have been short, and there are no long-term or maintenance studies.

Recommendations for Other Biological Treatments

(see Table 4.6)

- St. John's wort may be effective in treating depressive disorders of mild severity (Level 1 evidence) but is not recommended for more severe conditions (Level 2 evidence). While side effects are minimal, there is no regulation of *Hypericum perforatum* in Canada, and the drug-drug interactions are not known.
- Sleep deprivation is an effective transient treatment for depressive disorders (Level 2 evidence). Response may be maintained using medications (for example, antidepressants, lithium, or pindolol) or bright light (Level 2 evidence). Sleep deprivation may be most useful as an adjunctive treatment in hospitalized patients.
- Exercise alone may be effective in patients with mild depression (Level 2 evidence) and can be used as an adjunctive treatment to first-line treatments (Level 3 evidence).
- Limbic surgery (psychosurgery) has limited evidence for efficacy but may be considered for the most refractory and chronic cases (Level 3 evidence).
- Transcranial magnetic stimulation (TMS) and vagus nerve stimulation (VNS) are promising new biological treatments, but there is too little evidence to warrant recommendations for general clinical use (Level 2 and 3 evidence).

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