What to do if an initial antidepressant fails?

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ABSTRACT

OBJECTIVE To provide family physicians with practical ways of managing depressed patients responding insufficiently to initial antidepressant treatment.

QUALITY OF EVIDENCE A search of MEDLINE and relevant bibliographies showed most studies could be categorized as level III evidence. Few well controlled studies (eg, level I evidence) specify treatment of next choice in rigorously defined treatment-refractory depression (TRD).

MAIN MESSAGE Failure to achieve and sustain full symptom remission affects relatively few treated depressed patients. Most chronically depressed people are not absolutely resistant but are relatively resistant to treatment; they fail to achieve the goals of treatment because of improper diagnosis or insufficient treatment application. The literature on TRD has largely focused on medication strategies; fewer studies investigated psychosocial approaches. The best established augmentation strategies are lithium salts and triiodothyronine (T_3). Combination antidepressants have become clinical psychiatrists' preferred treatment, despite limited evidence. Electroconvulsive therapy (ECT) remains a feasible option for TRD, but response rates are poor among people with TRD. High relapse rates after ECT remain a serious and common clinical dilemma.

CONCLUSION Family physicians should familiarize themselves with some new strategies to modify inadequate response to initial antidepressant treatment.

RÉSUMÉ

OBJECTIF Fournir aux médecins de famille des moyens pratiques de traiter les patients déprimés qui ne répondent pas adéquatement à l'antidépresseur initial.

QUALITÉ DES PREUVES Une recension de MEDLINE et des articles pertinents a montré que la plupart des études étaient basées sur des preuves de niveau III. Peu d'études bien contrôlées (par ex., avec preuves de niveau I) indiquent un traitement alternatif spécifique dans les cas de dépression réfractaire au traitement (DRT) définie de façon rigoureuse.

PRINCIPAL MESSAGE L'incapacité d'obtenir et de maintenir une rémission complète des symptômes touche relativement peu de patients déprimés. Chez la plupart des patients souffrant de dépression chronique, la résistance au traitement est relative plutôt qu'absolue; l'objectif n'est pas atteint en raison d'une erreur de diagnostic ou d'un traitement insuffisant. Les travaux sur la DRT ont porté surtout sur les stratégies pharmacologiques et moins sur les approches psychosociales. L'ajout de triiodothyronine (T_3) ou de sels de lithium est la stratégie d'appoint la mieux fondée. L'utilisation d'une combinaison d'antidépresseurs est devenu le traitement de prédilection des psychiatres cliniciens, quoique l'efficacité de cette stratégie ne soit pas clairement établie. Le recours aux électrochocs (EC) est également possible, mais dans la DRT, le taux de réponse est faible. Le fort taux de rechute après l'EC demeure un dilemme clinique fréquent et grave.

CONCLUSION Le médecin de famille devrait se familiariser avec certaines des stratégies nouvelles susceptibles de corriger une réponse initiale inadéquate au traitement antidépresseur.

M ajor depression is an episodic, often disabling, chronic disorder.[1] Several investigations have concluded that at least 10% of patients in primary care have diagnosable mood disorders.[2] Approximately three quarters of "distressed high users" in general practice meet diagnostic criteria for major depression or generalized anxiety disorder.[3] Although antidepressant prescription has increased over the last decade, less than 20% of currently depressed people (or people experiencing a depressive episode in the past year) are at present receiving antidepressants.[1,4-7] The illness burden attributable to depressive illness is staggering and appears to be increasing. Depression is currently estimated to be the fourth leading cause of disability and premature death worldwide; it is projected to be second (behind ischemic heart disease) by the year 2020. Depression is already the leading cause of disability in some age groups (**Table 1**).[8]

Table 1. Ten leading causes of disabilities in 1990 for patients 15 to 44 years

RANK	DISEASE OR INJURY
1	Unipolar depression
2	Tuberculosis
3	Traffic accidents
4	Alcohol use
5	Self-inflicted injuries
6	Bipolar disorder
7	War
8	Violence
9	Schizophrenia
10	Iron-deficiency anemia

Data from Murray and Lopez.[8]

Quality of evidence
MEDLINE and relevant bibliographies were searched using MeSH words: refractory depression, augmentation, combination, electroconvulsive therapy (ECT), and psychotherapy. Most studies provided level III evidence (eg, case reports, case series, and open studies). Few well controlled studies (ie, level I evidence)

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attempted to specify treatment of next choice in rigorously defined treatment-refractory depression (TRD). Although empirically supported sequential treatment algorithms for TRD are not currently available, several carefully designed studies are under way.

Initial treatment of depressive disorders
For people who are diagnosed with depression and who receive acute treatment, response rates can be expected to approach 60% to 70%. Therapeutic outcomes in naturalistic settings are often noted to be less promising due to several modifiable deficiencies.[9,10] Therapeutic objectives in treating depression include full remission of symptoms, prevention of recurrence, and psychosocial and vocational restoration.[9,11] Most depressed patients who "respond" to antidepressants (eg, have fewer symptoms) fail to achieve full remission (eg, full abatement of symptoms).[12] It has recently been determined that residual "subthreshold" symptoms are present in most "responding" depressed patients and reflect ongoing disease. Residual symptoms portend recurrence of illness, chronicity, suicidal tendencies, cardiovascular disease, and psychosocial disability, and they powerfully predict increased use of health care.[11,13]

Dysthymic disorder is defined as a persistent depressed mood plus requisite symptoms for most days for at least 2 years (in children and adolescents it can be irritable mood for at least 1 year). The 12-month prevalence of dysthymia in primary care is 5%.[14] Duration of dysthymia, requisite number of syndromal symptoms (including depressed mood), and the necessity of the presence of depressed mood are partly helpful in distinguishing dysthymia from residual depressive symptoms. Often, the chronic course of residual depressive symptoms merges imperceptibly with dysthymic disorder. Complicating diagnosis further is the fact that 90% of dysthymic patients screen positive for either major depression or anxiety disorders at some time in their lives (although included in the appendix of the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders*, minor depression is not a diagnostic label commonly employed by psychiatrists).

Recurrence
When patients achieve full remission after acute treatment, at least 6 months of further maintenance treatment is recommended (longer-term therapy would be recommended for patients highly vulnerable to recurrence).[12] Several investigators have noted that 10% to 20% of antidepressant-adherent patients have

recurrence of depression within 6 months of the acute episode's remittance. These statistics imply that, in most cases (uncomplicated by comorbidity), people fail to achieve and sustain a fully remitted state.[11] This disquieting conclusion invites family physicians to become familiar with effective and safe optimization strategies for depression.

Treatment-refractory depression is a term often used imprecisely; the condition is frequently confused with chronic depression. Most people with chronic depression do not have TRD, as most have not received a single adequate trial of antidepressants. Furthermore, most patients labeled as TRD are not "absolutely resistant" to treatment; most have not received sufficient antidepressant application ("relative resistance" could be a more precise label).

Unfortunately, an empirically based "stepped-care" approach to patients insufficiently responding to the index trial is not available. This has led to confusion and controversy as to the "treatment of next choice." Fortunately, several adequately powered, well designed sequencing studies of TRD are under way. Until results from these and other studies are known, the approach to TRD remains largely empirical. This review attempts to provide family physicians with a practical approach to managing depressed patients who continue to have symptoms after an adequate initial trial of antidepressants.

Confirming diagnosis

Before embarking on alternate therapeutic avenues, a fundamental initial management principle is to confirm diagnosis of depression, reevaluate for medical or psychiatric comorbidity, identify concomitant medications that could exacerbate depression, and ensure patients have adhered to treatment (**Figure 1**).

Although a comprehensive review of the differential diagnoses for major depression is beyond the scope of this paper, we will note that observable characteristics of depression often overlap with those of common psychiatric and medical disorders (eg, bipolar disorders, thyroid disease, and anemia) (**Table 2**).

For example, many ambulatory bipolar patients are initially misdiagnosed with major depression, which can delay for many years a proper diagnosis and initiation of specific bipolar therapy.[15] Clinicians should inquire about prior hypomanic symptoms in all depressed patients. A recently published questionnaire helps clinicians detect bipolar disorder in depressed patients.[16]

Both population-based and clinical studies confirm a high rate of comorbidity in people with major

Table 2. Conditions phenotypically similar to major depression

Bipolar disorders

Anxiety disorders

Schizophrenia (negative symptoms)

Substance abuse or dependence

Bereavement

Adjustment disorders

Personality disorders

Medical disorders (eg, thyroid, anemia)

depression.[17-19] Often primary care patients with mixed anxiety and depressive syndromes receive only a diagnosis of anxiety as a symptom and comorbid disorder.[1] Moreover, depression is increasingly recognized to reciprocally and deleteriously affect the course and outcome of comorbid conditions. For example, presence of depressive symptoms (including subsyndromal symptoms) significantly increases the risk for cardiovascular morbidity and mortality in people with (and without) a history of cardiovascular disease.[20] Optimal treatment of depressed patients with comorbidity often requires specific and concurrent attention to both disorders.

An assortment of medications has been associated with onset of depression. The pathogenic relevance of medications ranges from low (eg, acetylsalicylic acid) to high (eg, steroids). Clinicians should inquire about all concomitant medications including over-the-counter and naturopathic preparations.
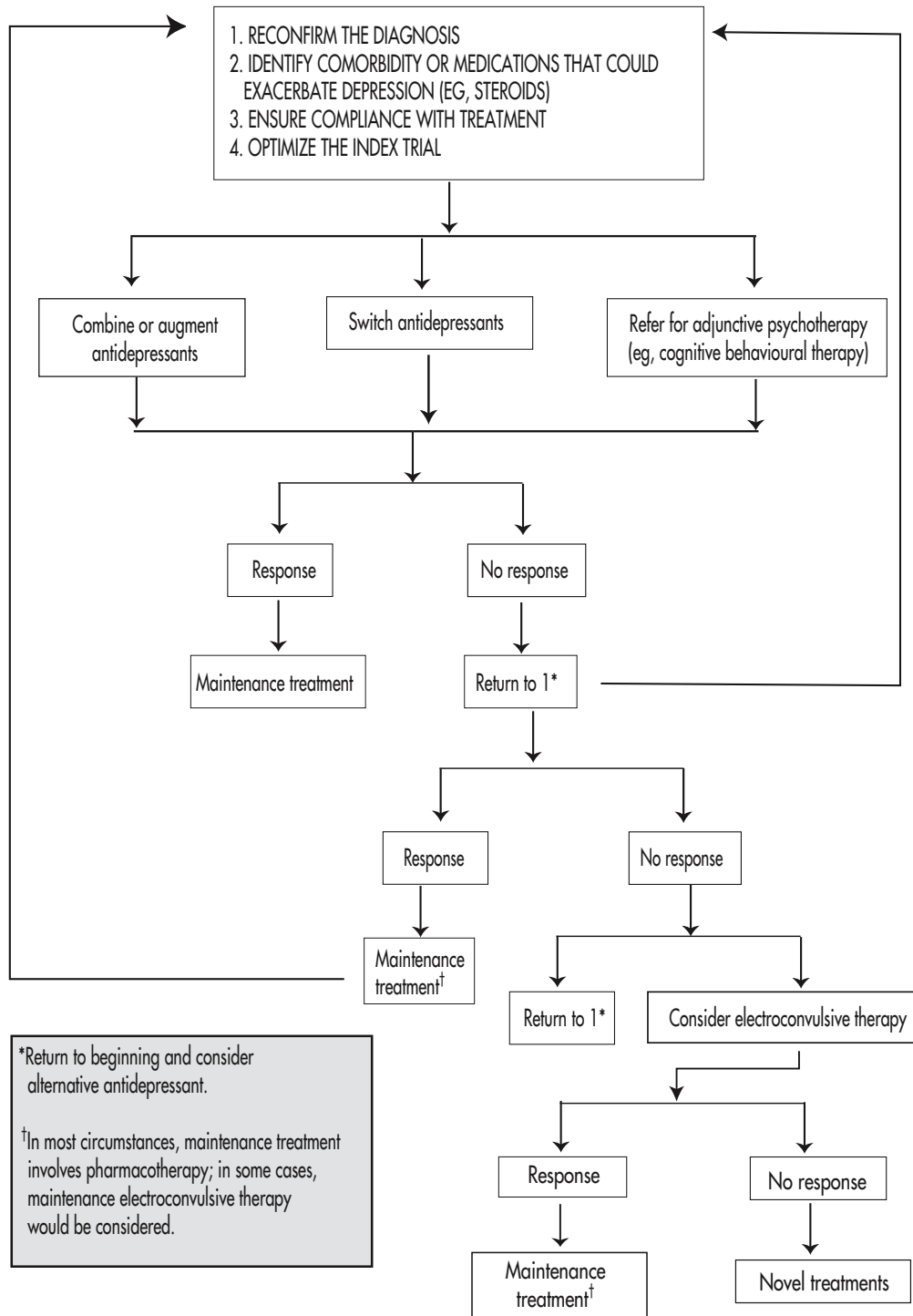
Most treated patients who begin antidepressant therapy discontinue treatment within 2 or 3 months.[12,21,22] It is disconcerting that most people who unilaterally stop treatment do not routinely inform their family physicians.[21] Clinicians must remember the importance of routine and systematic inquiry and education of patients.[9,12] Several relatively simple psychoeducational strategies have been demonstrated to enhance adherence to treatment (**Table 3**).[23-25]

Optimizing the index trial tacitly implies enhancing the dose and duration of therapy. When patients do not adequately respond to the index dose, the intensity of antidepressant treatment should be increased as tolerated (**Table 4**).[12]

An adequate duration of antidepressant treatment before dose adjustment is approximately 4 to 6 weeks.[26-29] Some patients are slower to respond (eg, people with chronic depression) or have poor tolerance, necessitating longer-term index treatment (eg, 6 to 12 weeks). Far too often elderly depressed

Figure 1. Treatment algorithm for depression resistant to initial antidepressant treatment

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                    ┌─────────────────────────────────────────────┐
                    │ 1. RECONFIRM THE DIAGNOSIS                    │
                    │ 2. IDENTIFY COMORBIDITY OR MEDICATIONS THAT   │
                    │    COULD EXACERBATE DEPRESSION (EG, STEROIDS) │
                    │ 3. ENSURE COMPLIANCE WITH TREATMENT           │
                    │ 4. OPTIMIZE THE INDEX TRIAL                   │
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Combine or augment antidepressants

Switch antidepressants

Refer for adjunctive psychotherapy (eg, cognitive behavioural therapy)

Response → Maintenance treatment

No response → Return to 1*

Response → Maintenance treatment†

No response → Return to 1* / Consider electroconvulsive therapy

Response → Maintenance treatment†

No response → Novel treatments

*Return to beginning and consider alternative antidepressant.

†In most circumstances, maintenance treatment involves pharmacotherapy; in some cases, maintenance electroconvulsive therapy would be considered.

Table 3. Psychoeducation strategies to enhance adherence to treatment

- Provide general information on depression: common signs, symptoms, and subtypes of depression. Websites, such as that of the National Depressive and Manic Depressive Association (**www.ndmda.org**), can be helpful.

- Discuss the importance of taking medication as prescribed and the implications of missed doses.

- Frequently inquire and educate patients about the type, severity, and duration of side effects.

- Tell patients to expect several weeks before symptoms improve; explore skepticism and resistance to therapy.

- Anticipate patient misinformation and dysfunctional beliefs about the illness or the treatment process. Explore both family and cultural attitudes toward psychiatric treatments.

- Instruct patients to continue taking medications when they are feeling better and describe the rationale for maintenance treatment.

Table 4. Dosing range for SSRIs and novel antidepressants: *For some depressed patients, dosing exceeds the usual effective dose range.*

MEDICATION	USUAL EFFECTIVE DOSE (MG/D)
SELECTIVE SEROTONIN REUPTAKE INHIBITORS	
Citalopram	20-40
Sertraline	100-200
Paroxetine	20-40
Fluvoxamine	100-200
Fluoxetine	20-40
NOVEL ANTIDEPRESSANTS	
Venlafaxine XR	75-225
Mirtazapine	15-60
Bupropion SR	150-300
Nefazadone	300-600
Moclobemide	400-600

Data from Kennedy et al.[12]

people receive inadequate doses of antidepressants or the duration of therapy is too short.[30]

Selective serotonin reuptake inhibitors (SSRIs) and the novel antidepressants are all first-line medications in Canada.[12] Medication should be individualized to patients, and several variables need to be considered, such as presence or absence of anxiety features, comorbidity (eg, generalized anxiety disorder), concomitant medications, earlier treatments, tolerance, cost, and patient preference. No convincing evidence shows that any currently available antidepressant is faster to onset than another. If there is no response

after 4 to 6 weeks of therapy, the dose should be increased. A recent managed care study concluded that only 11% of patients requiring antidepressant therapy received either adequate doses or appropriate length of therapy, despite the simplicity and frequent mention of the recommended first strategy.[27]

When initial treatment fails

After completing steps 1 to 4 in the algorithm presented in **Figure 1**, clinicians can follow two therapeutic avenues: to employ adjunct treatments or discontinue the index treatment and consider an alternative monotherapy. Combining treatments is increasingly popular and is somewhat imprecisely defined as *augmentation* (adding a treatment that is not approved as an antidepressant) or *combination* (combining two or more treatments approved as antidepressants).[31] Combining treatments could also imply adjunctive use of psychotherapy.

Augmentation and combination strategies for depression are carried out ostensibly for four reasons: to increase remission rates, to accelerate antidepressant response, to treat TRD, and to avoid adverse events with the index antidepressant. The benefits offered from combination approaches could derive from both pharmacokinetic and pharmacodynamic mechanisms.[31-33]

Augmentation and combination strategies have advantages in that they avoid the ill effects of discontinuing the initial antidepressant and offer a more rapid response. Moreover, the two best-studied augmentation drugs are generic and inexpensive. Additional cost is, however, a drawback when combining currently marketed therapies. Alternative antidepressant monotherapies are simpler, have lower risk of drug interactions, and have fewer side effects. When switching to an alternative antidepressant monotherapy, clinicians need to be familiar with the elimination half-life of the index treatment. This is particularly relevant when switching from fluoxetine to moclobemide or a non-selective irreversible monoamine oxidase inhibitor (MAOI), because of the long elimination half-life of the active metabolite norfluoxetine.

Generally, there is no need to stop one antidepressant for a time before starting another. Cross-titration is often well tolerated, but patients could develop additional side effects during the crossover period. The potential for synergism of adverse events (particularly serotonin-mediated tolerance) needs to be explained to patients. Serotonin syndrome has been described among people receiving agents that simultaneously

enhance central serotonin neurotransmission.[34] The combination of a serotonergic antidepressant with an MAOI or with moclobemide is generally avoided out of concern for serotonin toxicity.[35] Although not definitively established, the risk of serotonin syndrome could be less with other antidepressant combinations (eg, cross-titration from SSRI to serotonin noradrenaline reuptake inhibitor [SNRI]). If patients are intolerant of medications, a wash-out period should be considered. Periods of 2 weeks and 3 days when discontinuing an MAOI or moclobemide, respectively, are recommended (**Table 5**).[12,36]

Table 5. Augmentation strategies

AUGMENTATION DRUG	DAILY DOSE
Lithium*	600-900 mg
Triiodothyronine (T$_3$)	25-50 µg/d
Buspirone	30-60 mg/d
Psychostimulants (eg, methylphenidate SR)	10-60 mg/d
Novel antipsychotics (examples)	
• Olanzapine	5-20 mg/d
• Risperidone	0.5-2 mg/d
Tryptophan	1-3 g/d
Benzodiazepines (eg, clonazepam)	0.5-1.0 mg/d
Pindolol	2.5 mg three times daily

Aim for plasma levels of 0.5-0.8 mEq/L.

Augmentation

Somewhat surprisingly, the relative efficacy of augmentation (and combination) strategies is currently unknown. Lithium is the most investigated augmentation strategy. Lithium offers a primary antidepressant effect, particularly notable with—but not limited to—bipolar disorder. Although its popularity among family physicians is not overwhelming, lithium augmentation remains popular among Canadian psychiatrists when SSRIs elicit only partial response.[37] Most lithium augmentation studies have included older agents (tricyclic antidepressants, MAOIs); there are fewer (yet positive) studies of SSRIs and SNRIs.

Optimal lithium plasma levels for augmentation are approximately 0.5 to 0.8 mEq/L at 12 hours after administration. Recommended trial length is 2 to 6 weeks. If patients respond to an antidepressant-lithium combination, combination therapy should continue at least 6 to 9 months.[38] At this critical decision point, some clinicians elect to discontinue adjunctive treatment slowly. Unfortunately, the optimal duration of any augmentation or combination

strategy is not empirically established and needs to be determined on a case-by-case basis.

Thyroid augmentation has been demonstrated to both improve and accelerate antidepressant response in well controlled trials and meta-analysis.[39,40] Interestingly, thyroid augmentation might be more effective in female patients. Triiodothyronine (T$_3$), 25 to 50 µg/d, is preferred to thyroxine (T$_4$).[41] This dose rarely affects peripheral thyroid measures. Thyroid augmentation would be a logical treatment for depressed patients with low-normal thyroid levels who respond insufficiently to antidepressant treatment. Thyroid augmentation has not been evaluated highly by practising clinicians.[29,36] Although T$_3$ is rarely discontinued because of adverse events, it can increase anxiety, jitteriness, tachycardia, insomnia, and sweating. Moreover, thyroid hormone can increase atrial irritability or ventricular function (eg, contractile activity), which could lead to high output failure. Caution is paramount when prescribing these thyroid hormones to people with cardiac insufficiency or elderly people. High-dose T$_4$ treatment (not typically employed as an augmentation strategy) has been associated with osteoporosis after long-term treatment.[42]

No currently available data show whether long-term T$_3$ affects bone mineral density in patients with mood disorders. Concerns have been raised regarding supraphysiologic doses of T$_4$; treatment for 1 year or longer does not appear to influence bone mineral density substantially in premenopausal women but can adversely affect postmenopausal women with mood disorders.[43,44]

Buspirone is indicated for treatment of generalized anxiety disorder. Earlier investigations noted buspirone's efficacy as an augmentation strategy in heterogeneous samples of people with TRD. Although results from recent placebo-controlled trials in TRD have been less favourable, buspirone augmentation can shorten response times and improve core depressive symptoms.[45,46] Moreover, buspirone is a logical treatment for patients with prominent anxiety features (or comorbid generalized anxiety disorder) failing to benefit from an antidepressant. Buspirone's spectrum of therapeutic activity could extend to management of adverse events; it is sometimes effective as an antidote for SSRI-induced sexual dysfunction.[47]

Psychostimulants (eg, methylphenidate and dextroamphetamine) remain popular among some psychiatrists despite lack of placebo-controlled trial data. Therapeutic targets often include anergia, fatigue, and hyperphagia for depressed patients in general hospitals. Concerns include pharmacodynamic toler-

ance, abuse liability, and insufficient investigation in both academic and community settings.[42]

Novel antipsychotics (eg, olanzapine, risperidone, quetiapine) offer improved therapeutic profiles, when compared with older conventional antipsychotics. Interestingly, some appear to be useful as augmentation therapy for both psychotic and nonpsychotic depression inadequately responsive to an index antidepressant.[48,49] They are currently under active investigation.

Tryptophan has been demonstrated to decrease sleep latency, reduce awakening after sleep onset, and normalize sleep architecture. A modicum of high-quality scientific evidence confirms tryptophan's efficacy (versus placebo) as an augmentation strategy in TRD.[50] Tryptophan (1 to 3 mg/d) has been proven to accelerate response and to improve sleep parameters in patients treated with fluoxetine.[51]

Benzodiazepines are not routinely considered augmentation strategies. Their perils are well known to clinicians. Short-term, low-dose, judicious administration of some benzodiazepines (eg, clonazepam, 0.5 to 1.0 mg) in combination with SSRI treatment has been demonstrated to improve and accelerate response for core depressive symptoms, improve sleep, and reduce anxiety in SSRI-treated patients.[52] These benefits tend to be balanced, however, against the known risks of these compounds.

Pindolol has been demonstrated to accelerate antidepressant response but has not been proven as a reliable treatment for TRD and is not recommended for that purpose. There has been concern regarding the dose of pindolol (2.5 mg three times daily) in TRD studies as being too low.

Combining antidepressants

A variety of antidepressant combinations could theoretically be used; however, few adequately powered placebo-controlled trials of antidepressant combinations have been conducted with available first-line treatments in Canada. Bupropion combinations with SSRIs and SNRIs have become popular largely through the support of open trials.[29] Optimal doses of the respective antidepressants have not been definitely established. When bupropion is combined with usual doses of SSRIs or SNRIs, both agents have had acceptable tolerability. Clinicians might wish to begin bupropion at a low dose (eg, 100 mg/d) and increase as tolerated. Bupropion could have both pharmacokinetic and pharmacodynamic interactions with other agents administered concomitantly.[53] Despite the popularity of this strategy, its efficacy has not

been subject to adequately controlled investigations. Importantly, bupropion administration has been demonstrated to be useful for sexual dysfunction from SSRI or SNRI treatment.[54]

Another antidepressant combination gaining popularity is SSRI or SNRI coadministered with mirtazapine (**Figure 2**).[55] Mirtazapine appears to improve core depressive symptoms, reduce anxiety, and improve sleep efficiency when combined with these agents.

Figure 2. Combining antidepressants

SSRI or **SNRI** combined with **NaSSA**

SSRI or **SNRI** combined with **NDM**

SSRI combined with **TCA**

NaSSA—*noradrenaline and specific serotonin antagonist (eg, mirtazapine);*
NDM—*noradrenaline dopamine modulator (eg, bupropion);*
SNRI—*serotonin noradrenaline reuptake inhibitor (eg, venlafaxine);*
SSRI—*selective serotonin reuptake inhibitor; TCA—tricyclic antidepressant.*

Switching antidepressants

Although SSRIs are categorized together, they are pharmacologically heterogenous. Approximately 40% to 70% of patients failing to benefit from an initial SSRI could be expected to respond to a second SSRI. Subsequent SSRI response rates are higher if the index SSRI was discontinued due to poor tolerance as opposed to inefficacy.[56] A recently published trial has demonstrated acceptable response rates to citalopram in prospectively confirmed fluoxetine nonresponders. In that trial, fluoxetine was discontinued and citalopram was initiated on the following day. Tolerance was acceptable, and there were no serious adverse events.

Although insufficient evidence exists to guide treatment selection after index SSRI failure, some research implies that some SSRI nonresponders will benefit from a second SSRI. Switching to an antidepressant with a different neurochemical profile is, however, currently preferred over another "classmate SSRI" for patients not responding to an index SSRI.[12,57]

Psychotherapy

Cognitive behavioural therapy is a proven treatment for mild-to-moderate depression.[58-60] Three models for combining psychotherapy can be employed: concurrent, sequential, and crossover.[61] The advantages of each of these strategies have not been adequately investigated.

Cognitive behavioural therapy has been successfully combined (sequential and crossover) with antidepressant therapy in patients with chronic depression (concurrent) who are partially responsive to antidepressants and have high risk of recurrence (eg, multiple severe recurrences).[61] Although no data support psychotherapy as an effective treatment for highly medication-refractory patients, some data suggest that single medication failure does not necessarily imply subsequent psychotherapy failure.[60] Current psychotherapy research is attempting to further refine characteristics of patients and clinical factors that predict response to psychotherapy.

Electroconvulsive therapy

Electroconvulsive therapy (ECT) remains highly effective for people with TRD. Because ECT is often a treatment of last resort, acute efficacy is often compromised. Relapse rates exceed 50% in 1 year among people who do not receive maintenance medication.[62] In rare cases (eg, refractory treatment or poor tolerance) maintenance ECT is provided. For family physicians, the critical issue is when a patient should be considered for ECT. Some indicators for ECT are listed in **Table 6**.

Table 6. Possible indications for electroconvulsive therapy

- High acute suicide risk

- Severe physical deterioration

- Psychotic features

- Patient preference

- Refractory after at least two adequate trials of distinct classes of antidepressants and at least one attempt at augmentation or combination therapy

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Conclusion

Antidepressant treatments can offer important short-term efficacy. A sizable proportion of depressed patients fail to achieve optimal outcome with initial antidepressant selection. Unfortunately, few primary care patients receive optimization strategies,[22] which increases the risk of chronicity. Most cases of TRD are "relatively" resistant, as opposed to "absolutely" resistant, to treatment. Most depressed patients in primary care have not received one guideline-concordant antidepressant trial.[63] The various therapeutic avenues discussed in this review should improve outcomes. Few well controlled trials have been conducted in TRD. Current research attempts to determine a rational, evidence-based treatment approach to major depression. ❧

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Editor's key points
- Inadequate response to an initial antidepressant medication is a frequent and modifiable condition in primary care.
- First steps to address this are confirming the diagnosis, identifying comorbidity or possibly interacting medications, and checking compliance.
- Additional steps include increasing doses of antidepressant, augmentation (eg, lithium, T_3, buspirone), switching or combining antidepressants, and adding psychotherapy (eg, cognitive behavioural therapy).
- If these strategies fail, consider referral to a psychiatrist and possibly electroconvulsive therapy.

Points de repère du rédacteur
- Il est possible d'intervenir quand le patient ne répond pas adéquatement à la médication antidépressive initiale, une éventualité fréquente en pratique de première ligne.
- Il faut, dans un premier temps, vérifier le diagnostic, rechercher l'existence de comorbidité ou d'interactions médicamenteuses et s'assurer de la fidélité au traitement.
- Les autres mesures incluent l'augmentation de la dose d'antidépresseur, le recours à une stratégie d'appoint (par ex., lithium, T_3, buspirone), le remplacement de l'antidépresseur ou sa combinaison avec un ou plusieurs autres, et l'addition de psychothérapie (par ex., la thérapie cognitivo-comportementale).
- En cas d'échec de ces stratégies, on doit penser à demander une consultation en psychiatrie et à la possibilité d'électrochocs.