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CURRENT OPINION

Early Switching Strategies in Antidepressant Non-Responders: Current Evidence and Future Research Directions

Paul A. Kudlow · Roger S. McIntyre · Raymond W. Lam

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Abstract Studies have found that up to two-thirds of patients with major depressive disorder (MDD) do not fully respond to the first antidepressant. While switching antidepressants is a common strategy for antidepressant non-responders, there is still a lack of consensus about the optimal timing of a switch. Many clinicians wait for 6–12 weeks before considering a switch. The objectives of this paper are to (1) review the evidence for positive and negative predictive value (NPV) of early improvement at 2–4 weeks to predict final antidepressant response; (2) review randomized controlled trials (RCTs) that examine early switching strategies; and (3) provide future research directions and clinical recommendations for timing of antidepressant switching. We conducted a literature search for English-language studies via PubMed and Google Scholar, from 1984 to May 2013, with the following terms: 'antidepressants', 'MDD', 'time course', 'trajectory', 'early response', 'onset', 'delayed response', 'early improvement', 'predictors', 'switch', 'combination therapy', and 'augmentation'. Replicated evidence indicates that lack of early improvement (e.g. <20 % reduction in a depression scale score) at 2–4 weeks can be an accurate predictor to identify eventual non-responders. The NPVs suggest that only about one in five patients with lack of improvement at 4 weeks will have a response by 8 weeks. Three RCTs examined early switch strategies, but results are inconsistent and comparisons limited by methodological differences. Future studies should incorporate a standard consensus definition of early improvement, discern whether the effect of early switching is specific to certain types of antidepressants, and determine whether early switch is superior to other strategies such as augmentation or combination. Notwithstanding these limitations, there is reasonable evidence to recommend earlier assessment for improvement. If there is no indication of early improvement at 2–4 weeks after starting an antidepressant, and taking into account other patient and clinical factors, a change in management can be considered.

Key Points

Lack of early improvement, defined by <20 % reduction in a depression rating scale at 2–4 weeks, may be predictive of eventual clinical non-response to an antidepressant.

In the absence of early improvement, and taking into account side effects and other clinical factors, a change in management (increase dose, switch to another antidepressant, augment with another medication, add psychotherapy) can be considered.

There is still limited quality evidence comparing early switch strategies to continuing an antidepressant.

P. A. Kudlow
Department of Psychiatry, University of Toronto, Toronto, ON, Canada

R. S. McIntyre
University of Toronto, Toronto, ON, Canada

R. S. McIntyre
Head, Mood Disorders Psychopharmacology Unit, University Health Network, Toronto, ON, Canada

R. W. Lam (✉)
Department of Psychiatry, University of British Columbia (UBC) and Mood Disorders Centre of Excellence, UBC Hospital, 2255 Wesbrook Mall, Vancouver, BC V6T 2A1, Canada
e-mail: r.lam@ubc.ca

1 Introduction

According to clinical guidelines, antidepressant medications are considered among the first-line treatments for major depressive disorder (MDD) [1, 2]. While the evidence has shown that antidepressants are an effective treatment for moderate to severe MDD [3], naturalistic studies indicate that up to two-thirds of patients do not respond to the first antidepressant medication [4], with the chance of response decreasing and recurrence significantly increasing with subsequent treatment failures [5]. Most clinical guidelines recommend switching to another antidepressant as a first-line strategy for non-responders, although augmentation and combination strategies also have evidence to support their use. A salient clinical question remains: for patients who fail to respond to their initial antidepressant, what is the optimum time for switching? If patients are switched too early, they may needlessly abandon an effective medication; on the other hand, staying on an ineffective treatment will affect adherence and prolong suffering and impairment.

To date, a consensus still does not exist as to (a) when patients begin to improve after starting an antidepressant; and (b) how long patients should stay on an antidepressant before it is deemed ineffective. Evidence derived from older antidepressant studies suggested a delayed onset of therapeutic response [6–9], leading to the conventional belief that patients need to wait at least 8 weeks before concluding whether or not they are responding to an antidepressant [10]. However, recent reviews [10, 11] have summarized the many subsequent studies that showed an early onset (within 1–2 weeks) of antidepressant effects in ultimate responders, thereby contradicting the delayed-onset hypothesis and suggesting that responders can be identified earlier in the course of treatment.

Many studies have now examined whether early improvement, or lack of improvement, in depression symptoms can predict final clinical response. Most studies have defined 'early improvement' as $\geq$20 % reduction from baseline on a depression rating scale (e.g. Hamilton Rating Scale for Depression [HAM-D] [12], Montgomery Asberg Depression Rating Scale [MADRS]) [13], while 'clinical response' is typically defined as $\geq$50 % reduction from baseline. An early study of fluoxetine response found that early improvement at 2 weeks could predict 75 % of eventual responders [14]. Furthermore, other studies have suggested that lack of early improvement at 2 weeks may serve to reliably identify a subpopulation of non-responders [11]. Having this non-responder subpopulation wait 8–12 weeks before switching to another antidepressant may not be justified.

If early improvement can predict final response, how might this guide clinical decisions? One important clinical metric is the positive predictive value (PPV), which is the probability that a positive test (in this case, early improvement) actually results in a positive outcome (in this case, response at the end of the study). For clinicians, a more clinically relevant metric is the negative predictive value (NPV), which is the probability that a negative test (lack of early improvement) leads to a negative outcome (lack of response). A high NPV suggests that a response is unlikely with continued use of the antidepressant, and a change in management, such as switching to another medication, should be considered.

The objectives of this paper are to (1) review the evidence for predictive value of early improvement or lack of improvement for end-of-study response, focusing on studies examining PPV and NPV for current first-line antidepressants; (2) review controlled studies that examine the timing of early switching strategies; and (3) provide future research directions and clinical recommendations for timing of antidepressant switching.

A non-systematic review of the literature was conducted using PubMed and Google Scholar. The search included all English-language articles published between 1984 and May 2013. The following search terms were used: 'antidepressants', 'major depressive disorder', 'time course', 'trajectory', 'early response', 'onset', 'delayed response', 'early improvement', 'predictors', 'switch', 'combination therapy', and 'augmentation'. The terms were cross-referenced with each other to achieve the most comprehensive and relevant results. Bibliographies were also reviewed for further citations. Articles selected for narrative review were based on adequacy of sample size, the use of standardized experimental procedures, validated assessment measures, and overall methodological quality. We focused our review on studies involving newer antidepressants (selective serotonin reuptake inhibitors [SSRIs], serotonin norepinephrine reuptake inhibitors [SNRIs], bupropion, mirtazapine and agomelatine) because they are most commonly used in initial treatment.

2 Predictive Value of Early Improvement for Antidepressant Response

Table 1 summarizes the identified studies using early improvement to predict antidepressant outcome in which the PPV (13 studies) and/or NPV (15 studies) were reported or could be calculated from the results. For tabulation of NPV and PPV, we included only data for clinical response and definitions of early improvement based on change in a depression symptom scale. We chose to focus

Table 1 Studies of predictive value of early improvement for end-of-study outcomes

Author, year	Study design (duration)	*N*	Patient population	Antidepressant(s) used	Definition of early improvement	Outcome(s)	Responders at endpoint (%)	PPV	NPV
Nierenberg et al., 1995 [14]	Open-label trial (8 weeks)	143	Outpatients with HAMD-17 of ≥16 (mean 19.5)	Fluoxetine 20 mg	≥20 % reduction in HAMD-17	Response: ≥50 % reduction in HAMD-17	57	At 2 weeks: 75 % At 4 weeks: not reported	At 2 weeks: 64 % At 4 weeks: 81 %
Berlin and Lavergne, 1998 [37]	Post hoc analysis of two RCTs (8 weeks)	125	Inpatients and outpatients with mean MADRS score of 32.6	Study 1: mianserin mean dose, 71 mg/day; fluoxetine mean dose, 27 mg/day Study 2: mianserin 60 mg/day, fluvoxamine 150 mg/day	≥20 % reduction in MADRS	Response: ≥50 % reduction in MADRS	79	At 2 weeks: 92 %	At 2 weeks: 35 %
Nierenberg et al., 2000 [38]	Open-label trial (8 weeks)	182	Outpatients with HAMD-17 ≥16	Fluoxetine 20 mg	≥30 % reduction in HAMD-17	Response: ≥50 % reduction in HAMD-17	50	At 2 weeks: 26 % At 4 weeks: 46 %	At 2 weeks: 55 % At 4 weeks: 73 %
Baldwin et al., 2009 [39]	Post hoc analysis of 14 RCTs (at 8 weeks)	2,021	Outpatients	Escitalopram 10–20 mg	≥20 % reduction in MADRS	Response: ≥50 % reduction in MADRS	63	At 2 weeks: 79 % At 4 weeks: not reported	At 2 weeks: 57 % At 4 weeks: 78 %
Henkel et al., 2009 [40]	Naturalistic study (mean treatment duration: 59.8 ± 42.1 days)	795	Inpatients with mean HAMD-21 score of 25.1	SSRIs[a] SNRIs[a] Antidepressants + antipsychotics, mood stabilizers	≥20 % reduction in HAMD-21	Response: ≥50 % reduction in HAMD-21	80	At 2 weeks: 88 %	At 2 weeks: 37 %
Szegedi et al., 2009 [18]	Pooled analysis of 41 mirtazapine RCTs (37 trials = 6 weeks; 2 trials = 5 weeks; 2 trials = 8 weeks)	6,562	Inpatients and outpatients with HAMD-17 ≥22 (68 % of trials) and HAMD-17 <22 (32 % of trials)	Mirtazapine (52 %), SSRIs (21 %), TCAs (13 %), other[b] (14 %)	≥20 % reduction in HAMD-17	Stable Response: ≥50 % reduction in HAMD-17 at 4 weeks and subsequent weeks	Mirtazapine: 58 SSRIs: 58 TCAs: 63 Other: 55	At 2 weeks: 53 % Effect similar across medications	At 2 weeks: 89 % Effect similar across medications
van Calker et al., 2009 [41]	RCT (5 weeks)	124	Inpatients with HAMD-17 ≥16	Sertraline (mean final dosage of 90.2 mg/day) Amitriptyline or amitriptyline-N-oxide (mean final dosage was 175.4 mg/day)	≥20 % reduction in HAMD-17	Response: ≥50 % reduction in HAMD-17	Both groups had response rate >50 %. Overall rate not given	At 2 weeks: 56 %	At 2 weeks: 92 %
Kuk et al., 2010 [42]	STAR*D multicentre, open-label trial (at 6 weeks) [43]	2,280	Outpatients with HAMD-17 ≥14	Citalopram 20–60 mg	≥20 % reduction in QIDS-SR	Response: ≥50 % reduction in QIDS-SR	46	PPV not reported	At 2 weeks: 78 %
Kim et al., 2011 [44]	CRESCEND multicentre naturalistic study (up to 12 weeks)	568	Outpatients with HAMD-17 ≥14	SSRIs (48 %); newer antidepressants[c] (46 %); older antidepressants[d] (5 %)	≥20 % reduction in HAMD-17	Response: ≥50 % reduction in HAMD-17	56	At 2 weeks: 65 %	At 2 weeks: 67 %

Table 1 continued

Author, year	Study design (duration)	*N*	Patient population	Antidepressant(s) used	Definition of early improvement	Outcome(s)	Responders at endpoint (%)	PPV	NPV
Lin et al., 2011 [16]	Open-label trial (6 weeks)	131	Inpatients with HAMD-17 ≥18 and CGI-S ≥4	Fluoxetine 20 mg	≥20 % reduction in HAMD-17	Response: ≥50 % reduction in HAMD-17	52	At 2 weeks: 84 %	At 2 weeks: 84 %
Posternak et al., 2011 [8]	Open-label trial (at 8 and 12 weeks)	488	Outpatients; mean HAMD-17 = 17.6	Fluoxetine 20–60 mg	CGI-I ≤3	Response: CGI ≤2	8 week: 48 12 week: 57	PPV not reported	8-week response: At 2 weeks: 67 % At 4 weeks: 77 % 12-week response: At 2 weeks: 42 % At 4 weeks: 50 %
Uher et al., 2011 [19]	GENDEP [45] partially-randomized, open-label trial (8–12 weeks)	811	Outpatients; mean MADRS = 29.0	Escitalopram 10–30 mg, nortriptyline 50–200 mg	≥20 % reduction in MADRS	Response: >50 % reduction in MADRS	59	At 2 weeks: 75 %	At 2 weeks: 56 %
Bares et al., 2012 [46]	Naturalistic study (mean treatment duration: 4.9 ± 0.9 weeks)	71	Outpatients with MADRS of ≥20 and CGI of ≥4	Varying types and doses of antidepressants[e]	≥20 % reduction in MADRS	Response: >50 % reduction in MADRS	49	At 2 weeks: 71 %	At 2 weeks: 80 %
Gorwood et al., 2014 [47]	Multicentre naturalistic study (6 weeks)	2,938	Outpatients with QIDS-C ≥16 and CGI-S ≥4	Agomelatine 25–50 mg	≥30 % reduction in QIDS-C	Response: ≥50 % reduction in QIDS-C	55	At 2 weeks: 71 %	At 2 weeks: 69 %
Soares et al., 2014 [17]	Post hoc analysis of six RCTs (8 weeks)	2,274	Outpatients with HAMD-17 ≥20, mean (23.1) and CGI-S ≥4	Desvenlafaxine 50 mg	At 2 weeks: ≥25 % reduction in HAMD-17 At 3 weeks: ≥33 % reduction in HAMD-17	Response: ≥50 % reduction in HAMD-17	50	At 2 weeks: 70 %; At 3 weeks: 74 %	At 2 weeks: 68 %; At 3 weeks: 74 %

PPV positive predictive value is a measure of the degree to which early improvement can predict responders at endpoint, *NPV* negative predictive value is a measure of the degree to which lack of early improvement can predict non-responders at endpoint, *CGI-I* Clinical Global Impression-Improvement scale, *CGI-S* Clinical Global Impression-Severity scale, *HAMD-17* 17-item Hamilton Rating Scale for Depression, *HAMD-21* 21-item Hamilton Rating Scale for Depression, *MADRS* Montgomery-Åsberg Depression Rating Scale, *QIDS-C* Quick Inventory of Depressive Symptomatology, Clinician-Rated, *QIDS-SR* Quick Inventory of Depressive Symptomatology, Self-Report, *RCT* randomized controlled trial, *STAR*D* Sequenced Treatment Alternatives to Relieve Depression, *GENDEP* Genome-Based Therapeutic Drugs for Depression, *NaSSAs* noradrenergic and specific serotonergic antidepressants, *NDRIs* norepinephrine and dopamine reuptake inhibitors, *SARIs* serotonin antagonist/reuptake inhibitors, *SNRIs* serotonin and norepinephrine reuptake inhibitors, *SSRIs* selective serotonin reuptake inhibitors, *TCAs* tricyclic antidepressants

[a] Including: SSRI—citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline; SNRI—venlafaxine, duloxetine

[b] Including venlafaxine, trazodone, maprotiline

[c] Including bupropion, venlafaxine, mirtazapine

[d] Including amitriptyline, clomipramine, imipramine, milnacipran, nortriptyline, tianeptine, and trazodone

[e] Sample contained the following antidepressants, some monotherapy and some in combination: NaSSAs, NDRIs, SARIs, SNRIs, SSRIs, TCAs

on clinical response instead of remission to maximize comparisons across studies and because of variations in the definition of remission. In addition, remission rates vary depending on study duration, making it difficult to compare 6- to 12-week studies. We excluded two studies because they only included remission data [9, 15].

Most of the identified studies were open-label or naturalistic trials ($n = 10$ studies) or pooled meta-analyses of randomized controlled trials (RCTs; $n = 4$ studies) with sample sizes ranging from 71 to 6,562. The studies reported end-of-study response rates ranging from 46 % to 80 % after 6 weeks ($n = 6$ studies), 8 weeks ($n = 7$ studies), and up to 12 weeks ($n = 3$ studies). Early improvement was usually defined as at least 20 % reduction in HAM-D or MADRS ($n = 11$ studies). Two studies also examined optimum definitions of early improvement using receiver operating characteristic analysis [16, 17]. For early improvement at 2 weeks, PPVs were 26–84 %, while NPVs were 35–92 %. Five studies also included early improvement prediction at 3–4 weeks, with NPVs of 73–81 %. Moreover, the NPV was either higher or similar to the PPV in the majority of studies (10/15, 67 %), suggesting that NPV is a more reliable predictor. An example is the largest study, a meta-analysis of individual patient data ($n = 6{,}562$) from 14 RCTs [18], using early improvement (at least 20 % reduction in HAMD-17 at 2 weeks) as a predictor of stable response at 6 weeks. The PPV was relatively modest in that 53 % of early improvers became stable responders. However, the NPV was high at 89 %, indicating that only 11 % of patients without early improvement at 2 weeks became stable responders at 6 weeks.

In contrast, some studies have not found that early improvement predicted later response [8, 19]. For example, results of the partly randomized Genome-Based Therapeutic Drugs for Depression (GENDEP) study of escitalopram and nortriptyline ($n = 811$) determined that early improvement or lack of improvement at 2 or 3 weeks did not predict final response or remission at 12 weeks [19]. In the study, the timing of response was found to follow on a continuum; however, an accurate prediction of response only become clear following 8 weeks of treatment.

Despite these few discrepant studies, replicated evidence indicates that lack of early improvement at 2 weeks can be an accurate early predictor to identify eventual non-responders. The NPVs for 4 weeks are even higher than 2 weeks; only about one in five patients with lack of improvement at 4 weeks will have a response by 8 weeks. In the following section, we will examine the evidence for the optimal timing of treatment-switching strategies in this early non-improver MDD subpopulation.

3 Controlled Studies of Early-Switch Strategies

While the benefits of switching antidepressant medications after a failed trial have been investigated in many open-label studies and RCTs [20–22], only three studies have investigated the timing of switch strategies for antidepressant non-responders (Table 2). Nakajima et al. [23] completed a small sample ($n = 41$), randomized, open-label trial that showed benefits of an early-switch strategy versus maintaining the same antidepressant in individuals who did not show early improvement. Patients ($n = 132$) were initially treated with sertraline 50 mg; non-improvers (<20 % reduction in MADRS) at 2 weeks were randomized to 6 weeks in one of two groups: (a) sertraline was continued and titrated at 50–100 mg ($n = 21$); (b) sertraline was switched to paroxetine 20–40 mg ($n = 20$). For the primary outcome, the early-switch group showed a higher rate of responders than the continuing titration group (75 vs. 19 %; $p = 0.002$). In secondary outcomes, the early-switch group was also superior in the rate of remitters (MADRS ≤10) [60 % vs. 14 %; $p = 0.004$] and change in MADRS scores (19.0 vs. 7.5; $p < 0.001$). Of note is that these results may be limited by the differential dosing of the antidepressants, since maximal doses (40 mg) of paroxetine were possible while submaximal doses of sertraline were used.

In contrast, Bose et al. [24] found support for increasing the dose of the index antidepressant compared with an early-switch strategy. Severely depressed (MADRS ≥30 at baseline) patients with MDD ($n = 571$) received single-blind treatment with escitalopram 10 mg/day; non-responders (<50 % reduction in MADRS) at week 2 were randomized to 8 weeks of treatment with up-titration to escitalopram 20 mg ($n = 229$) or switch to duloxetine 60 mg ($n = 245$). At endpoint, there was no significant difference between conditions in the primary outcome, all-cause premature study discontinuations, or in MADRS response rates. However, the escitalopram up-titration group had significantly greater reduction in MADRS total score, as well as significantly higher remission rates (MADRS ≤10) than the duloxetine-switch group (54 % vs. 42 %, respectively; $p = 0.013$).

The third study examined an early (4 weeks) versus a more conventional (8 weeks) switch strategy in patients who did not show early improvement [25]. Patients with MDD ($n = 840$) were initially treated with escitalopram 10 mg. Patients who did not achieve early improvement (≤30 % reduction in HAM-D) at week 4 were randomized to switch to duloxetine (flexibly dosed at 60–120 mg/day) [early switch, $n = 282$] for 12 weeks, or continue on escitalopram (flexibly dosed at 10–20 mg/day) with non-responders (<50 % reduction in HAM-D) at week 8, switching to flexibly-dosed duloxetine (conventional

Table 2 Randomized controlled trials of early-switch strategies

Author, year	Study design (duration)	Randomized (*N*)	Baseline patient population	Switch strategy	Primary outcome	Results
Nakajima et al., 2011 [23]	Open-label RCT (8 weeks)	41	Inpatients and outpatients. No cutoff score was included as part of the inclusion criteria Patients were started on sertraline 50 mg/day for 2 weeks	Non-improvers (<20 % reduction in MADRS) to sertraline at week 2 were randomized to 6 weeks of (a) titration: sertraline was titrated at 50–100 mg; and (b) early switch: switched to paroxetine 20–40 mg	Response (≥50 % reduction in MADRS)	Positive primary outcome: early switch was superior to titration in rates of response (75 % vs. 19 %; $p = 0.002$) Secondary outcomes: early switch was superior to titration in change on MADRS at week 8 and rates of remission (MADRS ≤10) [60 % vs. 14 %; $p = 0.004$]
Bose et al., 2012 [24]	Double-blind RCT (10 weeks)	474	Outpatients with severe depression (MADRS ≥30) were started on escitalopram 10 mg/day for 2 weeks	Non-responders (<50 % reduction in MADRS) to escitalopram at week 2 were randomized to 8 weeks of (a) up-titration: escitalopram increased to 20 mg/day; and (b) early switch: switched to duloxetine 60 mg/day	Time to all-cause premature study discontinuation	Negative primary outcome: no difference in time to all-cause discontinuation between groups Secondary outcome: up-titration was superior to early switch in change on MADRS at week 8 and rates of remission (MADRS ≤10) [54 % vs. 42 %; $p = 0.013$]; no difference between groups in rates of response
Romera et al., 2012 [25]	Double-blind RCT (16 weeks)	566	Outpatients with HAMD-17 ≥19 and CGI-S ≥4 were started on escitalopram 10 mg/day for 4 weeks	Non-improvers (<30 % reduction in HAMD-17 at 4 weeks were randomized to 12 weeks of (a) conventional switch: 4 further weeks on escitalopram 10–20 mg/day, then, for non-responders (<50 % reduction in HAMD-17), switch to duloxetine 60–120 mg/day for 8 weeks; responders continued on escitalopram; and (b) early switch: switch to duloxetine 60–120 mg/day for 12 weeks	Time to confirmed response and time to confirmed remission (HAMD-17 ≤7 for at least 2 consecutive weeks)	Negative primary outcomes: no differences in time to confirmed response or confirmed remission between groups Secondary outcome: early switch was superior to conventional switch in change on HAMD-17 at week 8 and rates of confirmed remission (43 % vs. 36 %; $p = 0.048$); no difference between groups in change on HAMD-17 at week 16 and rates of confirmed response

RCT randomized controlled trial, *MADRS* Montgomery-Åsberg Depression Rating Scale, *HAMD-17* 17-item Hamilton Rating Scale for Depression, *CGI-S* Clinical Global Impression-Severity scale

switch, $n = 284$) for another 8 weeks. Hence, the conventional-switch group was composed of patients who responded to escitalopram and stayed on the medication for 16 weeks ($n = 83$), and those who were on escitalopram for 8 weeks and duloxetine for 8 weeks ($n = 165$). At the end of 16 weeks, there were no statistically significant differences between the two strategies in the primary outcomes, time to confirmed response (≥50 % reduction in HAM-D for at least 2 consecutive weeks) or confirmed remission (HAM-D ≤7 for at least 2 consecutive weeks). However, those subjects randomized to the early-switch strategy achieved significantly greater confirmed remission rates compared with the delayed switch group (43 % vs. 36 %, respectively; $p = 0.048$). A pre-specified subgroup analysis examined patients with pain at baseline ($n = 434$) [26]. Those in the early-switching group ($n = 138$) were found to have significantly lower visual analogue scale mean pain levels for overall pain, headache, back pain, shoulder pain, interference with daily activities, and time being awake in pain compared with the delayed-switching group ($n = 89$). Moreover, time to achieving normal functioning (Sheehan Disability Scale total score ≤6 [27]) was shorter in the early-switching group ($p = 0.042$) [26].

In summary, a small study found that an early switch (at 2 weeks) from sertraline to paroxetine led to superior outcomes compared with continuing on sertraline [23]. In contrast, both larger studies had negative results for primary outcomes for an early switch; only on analysis of secondary outcomes did some benefits of different strategies become apparent. However, one study found superior secondary outcomes for up-titration of escitalopram compared with early switch to duloxetine [24], while the other found superior outcomes for early switch (at 4 weeks) to duloxetine compared with a conventional switch (at 8 weeks) strategy [25].

4 Limitations of the Evidence

Unfortunately, it is difficult to reconcile the results of these studies because of differences in methodology, including the definitions of early improvement, the timing of switch decisions, the type of antidepressant switches, and the primary outcomes. Lack of early improvement, and the randomization to switch, was defined as <20 % reduction in MADRS at 2 weeks [23], <50 % reduction on the MADRS at 2 weeks [24], and <30 % improvement on the HAM-D at 4 weeks [25]. One study switched from one SSRI to another [23], while the other two involved SSRI to SNRI switches. The question of whether a switch within an antidepressant class is superior to switching to another class is still in doubt. A recent study [28] indicated that in patients unresponsive to SSRIs, changing to antidepressants with different mechanisms of action may be a more effective switching strategy. Generally, however, systematic reviews and large RCTs have either shown no differences [20, 21] in switching from one SSRI to another versus a different class, or small differences of questionable clinical significance [22].

5 Future Research Directions

Given the limitations and inconsistent findings of the few studies investigating early-switch strategies, further RCTs are needed to replicate and clarify these data and to discern whether any benefits of early switching are specific to within-class or between-class switches. Notwithstanding, there is still a lack of consensus as to whether early improvement with antidepressants is specific to certain mechanisms of action, or common across medications. Given the lack of consensus, additional RCTs that directly compare dissimilar antidepressants (e.g. SSRIs versus SNRIs versus other newer agents, etc.) are needed in order to determine whether class/mechanism of action affects onset of antidepressant effects. Future studies should incorporate a standard consensus definition of early improvement.

There are also no studies to date that have examined the timing of other commonly practiced treatment interventions such as augmentation with lithium or atypical antipsychotics, or combination antidepressant therapy. Rigorous RCTs are needed in order to determine the clinical benefits associated with the optimal timing of these treatment interventions compared with switch strategies.

While traditional clinical scales, such as the HAM-D and MADRS, may be sufficient for detection of overall symptom improvement, they may not be the optimal scales for detecting early improvement. Some symptom items (e.g. insomnia) are prone to improve or worsen early in treatment as a consequence of side effects of the antidepressant, and hence will confound the assessment of early improvement. There is also some evidence that certain depressive symptoms may improve earlier and to a greater extent than other core symptoms [11, 15, 29]. Further research into new clinical metrics, possessing greater item sensitivity and specificity for detection of these early effects of antidepressant therapy, is required. Self-rated scales (e.g. the Quick Inventory for Depressive Symptomatology, Self-Rated [QIDS-SR] [30]), which are more feasible to use in busy clinical practice settings, should also be examined in addition to clinician-rated scales. Additionally, studies have focused on prediction of eventual symptom-based definitions of clinical response or remission. Because there is increasing recognition that functional improvement and quality of life are more important than

symptom improvement as a treatment outcome for patients with MDD [31, 32], future research should also examine early symptom improvement as a predictor of functional and quality-of-life outcomes.

A high priority for future research is to identify biomarkers (e.g. genetic, genomic and proteomic factors, neuroimaging, electroencephalography, polysomnography [33], etc.) of early improvement and to determine whether these can help predict response trajectories and identify those patients who would most benefit from early treatment switches. For example, a recent RCT provides evidence for using functional neuroimaging (i.e. changes in insula metabolism) as a 'treatment-specific biomarker' which can be used as an objective guide for whether to initiate pharmacotherapy or cognitive behavioral therapy in individuals with MDD [34]. Additional studies to elucidate other biomarkers of early improvement and prediction of treatment response are currently underway [35].

6 Conclusions and Clinical Recommendations

The findings from these various studies support the principles of measurement-based care, or the routine use of clinical scales, to properly assess for early improvement and response trajectories. Notwithstanding the limitations described, there is sufficient evidence to recommend earlier assessment for lack of improvement. If there is no indication of early improvement (e.g. <20 or <30 % reduction in depression rating scale scores) at 2–4 weeks after starting an antidepressant, a change in management can be considered. The decision for a change, or to continue 'watchful waiting', must also take into account other patient and clinical factors, including the severity of depression, need for rapid improvement (including risk for suicidality and severe functional impairment), psychosocial context and complicating stressors or life events, side effects experienced, physical or psychiatric comorbidities, and patient preference. A change in management could include increasing the dose of antidepressant, switching to another antidepressant, augmenting with another agent, or adding a non-medication treatment such as psychotherapy. If the decision is made to switch antidepressants, care should be taken to avoid discontinuation syndrome by tapering (reduction or increase of regimen dose/frequency over time) or cross-tapering antidepressants (one antidepressant is tapered down while the new antidepressant is tapered up over the same period of time) [36].

Results of future research may allow for a more personalized approach to the treatment of MDD as it may help to inform clinicians as to which individuals may benefit from early pharmacological treatment interventions (i.e. switch, combination, augmentation), non-pharmacological approaches, or those who would alternatively benefit from staying the course. Similarly, a validated biomarker to identify people who will not benefit from an ongoing antidepressant treatment at the earliest possible occasion could minimize unnecessary drug exposure and suffering.

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