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Going Beyond Antidepressant Monotherapy for Incomplete Response in Non-Psychotic Late-Life Depression: A Critical Review

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Abstract

Many older adults with Major Depressive Disorder (MDD) do not respond to antidepressant monotherapy. While there are evidence-based treatment options to support treatment beyond monotherapy for adults, the evidence for such strategies specifically in late-life MDD is relatively scarce. This review examines the published data describing strategies for antidepressant augmentation or acceleration studied specifically in older adults, including lithium, stimulants, and second-generation antipsychotics. In addition, the authors suggest strategies for future research, such as study of specific agents, refining understanding of the impact of medical or cognitive comorbidity in late-life depression, and comparative effectiveness to examine methods already used in clinical practice.

Keywords

antidepressant; pharmacotherapy; augmentation; depression

Introduction

Late-life depression (LLD) is prevalent and the absolute burden of illness will increase as the population ages. It is associated with additional morbidity and mortality independent of medical illness (1, 2), attempted and completed suicide (2), and also worsens prognosis related to medical illness (3–5). The association between depression in older adults and functional disability has been characterized, generally demonstrating a positive correlation between severity of symptoms and disability (6). Other work suggests that depressive

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symptoms are actually associated with the onset of physical disability when controlling for baseline health and social status (7)

There has been a sustained effort to improve rates of treatment and to facilitate guideline-adherent care for older adults. Much of the focus has been on the delivery of care management strategies in primary care settings to, among other things, ensure antidepressant (AD) trials of adequate dose and duration (8–10). Reviews of AD efficacy and effectiveness in late-life depression confirm that AD medications are more effective than placebo, though remission rates to SSRI or SNRI monotherapy are relatively lower than one might hope, ranging from 28 to 44% (11, 12). Response may be slower and the risk of relapse higher than observed in younger adults (13), while those older patients who achieve remission following initial treatment with psychotherapy and AD monotherapy are then less likely to have recurrent depression on maintenance pharmacotherapy (14).

While the syndrome of Major Depressive Disorder describes a constellation of symptoms that likely result from multiple etiologies, LLD is an even more heterogeneous condition. As reviewed by Alexopoulos, depressive symptoms may arise in the context of medical and neurological disorders and are possibly reciprocally linked: they may precede cognitive decline or dementia; late-onset MDD differs from early-onset MDD in family history of mood disorders (lower) or dementia (higher); and cerebrovascular disease may “predispose, precipitate, or perpetuate” some late-life syndromes (15). Given the clinical heterogeneity of LLD, Mulsant and Pollock propose a number of diagnostic variables that should be considered, especially when encountering treatment-resistance, including incipient dementia, comorbid medical conditions, and psychotic features (16). Importantly, however, despite the complex nature of LLD, studies of sequential treatment suggest that patients may achieve remission, such as 1996 work from Flint and Rifat (17) where 61% responded to the first medication (nortriptyline), while 64% of the remaining group responded to additional treatment trials, and a three-year trial by Kok et al, with complete remission in 84% of their sample (18). The STAR*D trial of non-psychotic MDD, which while not limited to older adults did include them (age range from 18–75 years), also demonstrated the importance of sequential treatment, with cumulative remission increasing from around 33% after one trial to 67% after four (19). However, the key limitation of all these sequential treatment trials is that, without inclusion of a placebo-control group, it is not possible to distinguish the effect of modifying pharmacotherapy from that of prolonging the duration of the initial treatment.

Sequential treatment, while including antidepressant switches, various adjunctive strategies, and possibly culminating in electroconvulsive therapy, frequently features the addition of a second medication to an antidepressant. STAR*D, while highlighting the importance of sequential treatment to achieve remission, also demonstrated that augmentation is a popular treatment strategy despite limited empirical evidence (20). Confirming this observation from STAR*D, pharmacoepidemiology among the general population shows that addition of medications to antidepressant monotherapy is common and rates of psychotropic polypharmacy continue to rise (21, 22). In their recent study of prescribing by office-based psychiatrists between 1996 and 2006, Mojtabai and Olfson describe a significant increase in the use of AD combinations as well as the use of antipsychotics as adjuncts to AD therapy prescribing. Given limited response and remission rates to AD monotherapy and the well-documented association of depressive symptom burden with morbidity and mortality, it is conceivable that clinicians treating their older patients with depression are likewise increasing their prescription of complex treatment regimens. Various strategies have been studied in mixed age populations such as AD combinations (23, 24) or augmentation of an AD by other pharmacologic means including lithium (25, 26), triiodothyronine (27, 28), and second-generation antipsychotics (29). However, given pharmacokinetic and pharmacodynamic changes in the elderly (30, 31) and the fact that older patients are under-

represented in or even specifically excluded from clinical trials, results of controlled trials of combination and augmentation strategies may not be generalizable to older adults.

The aim of this review is to examine and summarize what, if any, evidence exists for pharmacologic treatment beyond AD monotherapy for incomplete response in unipolar, non-psychotic LLD.

Methods

For this review, a search for evidence-based guidelines for pharmacotherapy added to antidepressant monotherapy in older adults with Major Depressive Disorder (MDD) was performed on January 31, 2011, using the National Guideline Clearinghouse database, the Agency for Healthcare Research and Quality Evidence-based Practice Reports database, and the Cochrane Database of Systematic Reviews, which yielded no publications. In addition, relevant studies published in English were sought with MEDLINE searches using “antidepressant,” “older adults”, and either “combination”, “augmentation”, or “adjunctive”. The references of all works were then hand-searched for any additional sources. While studies that exclusively focused on bipolar or psychotic depression were excluded, a small number include patients with bipolar or psychotic depression and they are included.

For the purposes of this paper, we use “augmentation” to mean the addition of a second agent following incomplete response to antidepressant monotherapy in an attempt to achieve remission. In the majority of the studies included, the augmenting agent is not thought to be an antidepressant itself (e.g., lithium carbonate), though a subset do utilize addition of a second FDA-approved antidepressant. Some studies included begin acute-phase treatment with both an antidepressant and the augmenting agent (e.g., methylphenidate) specifically to speed response. We use “acceleration” to describe this strategy. Articles will be summarized by evidence into Class I (randomized, controlled trials), Class II (well-designed observational studies with concurrent controls such as cohort or case-control), and Class III (expert opinion, case series, case report, and studies with historical controls) (32).

Agents for Partial Response

To date, there is no Class I evidence for augmentation of partial response (Table 1) in late-life depression. Most of the evidence to date comes from case series or non-randomized clinical trials without benefit of a placebo arm.

Initial reports of AD augmentation in the elderly focused on lithium carbonate for partial response, which was thought to be an effective and rapid strategy augmentation strategy based on initial work in a younger population with depressive illness (26). The first publication describing lithium augmentation in older persons was a small case series (N=5) in 1986 (33), followed by two more retrospective case series by Lafferman et al. (N=14) (34) and Finch and Katona (N=9) (35) that decade. Each reported a positive response for a majority of cases using lithium carbonate to augment AD monotherapy, generally with a tricyclic antidepressant or a closely related drug, with “complete” or “good” improvement reported in 50–100% of cases. In 1990, van Marwijk et al. (36) published the largest retrospective case series of lithium augmentation, which included 51 cases. This was the first series to consider adequacy and efficacy of previous AD treatment, defined as previous treatment with at least 75mg of imipramine or equivalent dosage during a period of at least 4 weeks. While the first four reports of lithium were uniformly positive, it is difficult to generalize the results given diagnostic heterogeneity, variation in type and duration of initial pharmacotherapy, a wide range of serum lithium levels across studies (0.15–1.3 mEq/L), and unclear duration of augmentation.

The first prospective studies of lithium augmentation for partial response in the elderly found less promising results than suggested in earlier retrospective studies. While neither was placebo-controlled, these were the first to use clear, measurement-based criteria for response or lack thereof. The first prospective study of AD augmentation was published in 1991 by Zimmer et al (37), which used inclusion criteria of scale-based measurements (HRSD-17) to enroll partial or nonresponders (N=15) after four weeks of pharmacotherapy with a steady-state nortriptyline plasma level between 50 and 150 ng/ml. They continued nortriptyline with the addition of lithium, with a goal serum level of 0.3–1.0 mEq/L. While their overall response rate (67%) was similar to that reported by van Marwijk et al. (36), Zimmer et al. found a lower proportion of complete responders, at just 20%. This study improves on previous augmentation efforts by clearly defining criteria for treatment failure. Nevertheless, requiring only four weeks of monotherapy at adequate plasma levels is likely to be too brief given the possibility of further response to a longer course of nortriptyline monotherapy (13); without a placebo group, it is difficult to argue that response in the three complete responders was due to the augmentation. Alternatively, the three-week augmentation period was too short to realize the full benefits of lithium, leading to a possible underestimation of the benefits of this strategy.

Flint and Rifat (38), published the second prospective trial of lithium augmentation (N=21) and the first in an exclusively unipolar depressed population without psychotic features. In addition, it was the first trial that involved a selective serotonin reuptake inhibitor (SSRI) as one of the initial pharmacotherapy options. The rate of complete responders (24%) was similar to the rate reported by Zimmer et al., though there were far fewer partial responders (14%), possibly related to the more stringent HRSD-17 criteria defining response as 8 rather than 10. Unfortunately, the authors did not report rates of response by initial medication class, which included nortriptyline, fluoxetine, and phenelzine. They did report that 10 of 21 (48%) developed adverse events during lithium augmentation (“neuromuscular or neurologic”), including all four patients on fluoxetine, in contrast to Zimmer et al., who did not comment on side effects.

The largest prospective reports of augmentation in late-life depression both come out of the acute treatment phase of the Maintenance Therapies in Late-Life Depression study conducted at the University of Pittsburgh Medical Center. The first (N=53) was published by Whyte et al. in 2004 (39), in which the addition of bupropion SR, lithium, or nortriptyline was compared to switching to venlafaxine XR for older adults with MDD who had either not responded or relapsed following at least 12 weeks of treatment with paroxetine and interpersonal therapy (IPT). While 51% of subjects discontinued at least one augmentation trial due to side effects—most commonly tremors, dizziness, and unsteadiness, and augmentation with bupropion SR associated with the highest rate of discontinuation—with sequential trials, the cumulative response rate reached 60% (in contrast to 42% response for subjects who switched to venlafaxine XR). This report was followed by a closer analysis (N=69) of the likelihood, speed, and predictors of recovery in older adults receiving augmentation pharmacotherapy published in 2007 (40). This work demonstrated that the rate of recovery with augmentation following either inadequate response (24 of 48, 50%) or early relapse (14 of 21, 66.7%) was lower than in those who never required augmentation (78 of 90, 86.7%), while those who received augmentation reported the highest level of side effects, controlling for recovery. Overall, augmentation raised the recovery rate from 40.0% to 59.5%. However, without a placebo comparison group, it is unclear whether this increase in recovery can be attributed to the various augmentation strategies as opposed to simply the passage of time on continued AD therapy.

One more important piece of evidence for lithium augmentation came in 2007 with the first randomized, controlled trial comparing lithium augmentation to a switch to phenelzine after

AD monotherapy (41). In this trial (N=29), patients who had not achieved remission after at least four weeks of a TCA or venlafaxine XR were randomized to either six weeks of lithium (target level 0.6–1.2 mEq/L) or switch to phenelzine (up to 60mg/d) following a wash-out period. While remission rates were relatively low with either strategy, lithium augmentation was statistically superior despite the small sample size, with remission for 5/15 (33%) compared to 0/14 (0%) on phenelzine. The average lithium level during the trial was 0.71 mEq/L, with no patients dropping out or discontinuing a medication due to side effects. Of note, this is one of the only reviewed studies to explicitly address medical comorbidity, and the lithium group had a better outcome despite a higher mean number of medical diagnoses and somatic medications than the phenelzine group.

Since first described in 2001 (42), a number of studies have examined the benefit of AD augmentation with second generation antipsychotics (SGA) in mixed-age samples. A recent meta-analysis demonstrates that SGAs in the adult population are significantly more effective than placebo, though adjunctive SGA therapy is associated with higher discontinuation due to adverse events (29). The first study of SGA augmentation for LLD (43) was a prospective, open-label pilot trial (N=20) of aripiprazole augmentation for non-remitters after 6 weeks of SSRI monotherapy. One-half of the group (10 of 20) met criteria for remission after six weeks of aripiprazole. Another pilot study of open-label aripiprazole augmentation in LLD, which yielded similar results, was published in 2009 (44). Sheffrin et al. enrolled partial or non-responders (N=24) to sequential trials of escitalopram followed by either duloxetine or venlafaxine for 12 weeks. Following 12 weeks of aripiprazole augmentation, 50% (12/ 24) met criteria for remission. This improvement is particularly notable given 29.1% of participants were in the partial response group at the time of initiating augmentation, perhaps decreasing the likelihood of demonstrating significant improvement during augmentation. In addition, prior to augmentation, all participants had received a total of 28 weeks of AD therapy, with the last 12 (of 28) weeks of therapy with a SNRI (either venlafaxine or duloxetine). In several studies previously discussed, the period of monotherapy was sufficiently brief that subsequent benefit of augmentation was difficult to separate from improvement that could be expected from longer monotherapy. The duration of sequential SSRI and then SNRI monotherapy makes it easier to attribute subsequent benefit to the augmentation strategy. The 12 remitted subjects were followed for a median of 27.6 weeks: none experienced a relapse of a major depressive episode and body mass index was stable over six months of continuation pharmacotherapy. Neither the Rutherford nor Sheffrin studies comment on impact of medical comorbidity in comparing responders to non-responders. While only supported by two open-label pilot studies, the preliminary work on aripiprazole has been promising and there is now a full-scale, multi-center randomized controlled trial of aripiprazole augmentation underway (45).

Agents for Acceleration

A small number of studies (Table 2) in late-life depression have explored the utility of augmentation to speed anti-depressant response in late-life, given work suggestion that late-life depression may be slower to respond to treatment (13). The majority of this work comes from a series of pilot studies of methylphenidate (MPH) augmentation by Lavretsky and colleagues beginning in 2001 (46–48). The first two studies (N=10 and 11) were prospective, open-label trials of citalopram augmented with MPH. Both trials demonstrated a reduction of symptoms within just two weeks, with three (27%) patients in the latter achieving remission by week 2 and a majority in both studies in remission by week 8. These two open-label trials were followed by a small, double-blind, placebo-controlled trial (N=16) published in 2006 (48). This suggested that MPH in combination with citalopram could lead to rapid improvement of symptoms in depressed older adults, in a population where 13 of 16 patients had episode length of at least 24 months when the trial began. At

week 8, the mean change in HDRS compared to baseline between MPH and PBO groups was -16.8 and -12.2 , respectively, with between group difference of 6.2 ($p = .05$; Cohen's d of 1.25). A majority of patients in both PBO and MPH groups reported side effects (66% and 80%, respectively), with three subjects in MPH group dropping out due to side effects while none in the PBO group dropped out. While the pilot MPH work suggests this as a possible augmentation strategy, the small size limits the conclusions that can be drawn with regards to the utility of methylphenidate.

Maintenance of Augmentation Medications following Remission

While elderly patients may benefit as much as midlife patients from aggressive treatment of depression, it may be that they also have an inherently high risk of relapse (13), making investigation of maintenance therapy in late-life depression an important topic (Table 3). The first report on augmentation discontinuation was published by Reynolds et al. in 1996, part of an ongoing trial of maintenance therapies in LLD. In this study of combined nortriptyline and IPT in 158 patients, 39 required and agreed to acute-phase augmentation given HRSD-17 >10 following at least 8 weeks of nortriptyline therapy. A variety of strategies were available to and selected by the patient and treating physician: augmentation with lithium carbonate (0.5–0.8 mEq/L), perphenazine (median dose 4mg/d), or both; sequential addition of lithium and paroxetine; or combination paroxetine alone. The additional medication was continued until patients met study criteria for response, after which it was tapered and gradually discontinued over 3–4 weeks. 25 of 39 (64.1%) of those requiring additional medication ultimately responded, but then 52.0% (13 of 25) of those responders relapsed during the continuation phase when augmentation was discontinued. This was a much higher rate of relapse than the 6.1% (6 of 99) in the non-augmentation group, suggesting that those who require augmentation during acute-phase treatment may require continuation of the additional agents to help maintain response.

The second study of augmentation discontinuation was a much smaller study conducted by Hardy et al. in a population that had responded to lithium augmentation of TCA partial-response and had been symptom-free for at least one year (49). While small ($N=12$), it was prospective with the lithium withdrawn in a double-blind, PBO-controlled fashion. The side effects of lithium may have clued clinicians and patients into whether they were receiving lithium or PBO, though the relatively low level (0.4 mEq/L) may have made this distinction less obvious. 2 of 4 maintained on lithium had a recurrence, while 2 of 5 on placebo had recurrence. Given the very small number of patients, it is difficult to draw conclusions from the relapse rates, though the results do not clearly point to the value of longer-term lithium augmentation. Perhaps most notably, the lithium group reported significantly more side effects at all clinic visits beyond baseline, including urinary and neurological symptoms, despite the relatively low average lithium level.

One last study of lithium augmentation discontinuation was published in 2001 (50). This was a naturalistic, prospective study ($N=21$) in a population with unipolar depression that was “clinically well” with combined AD plus lithium treatment. There are a number of potential criticisms, including lack of detail on duration of AD treatment pre- and post-augmentation and no criteria for relapse provided. Lastly, there was a selection bias where those known to have relapsed off lithium previously were not considered for discontinuation. Eleven of 21 (52.4%) patients relapsed following lithium discontinuation, and those that relapsed had been on lithium longer (2.5y) than those that remained well (1.4y), a statistically significant difference. There is no discussion of side effects and, if present at baseline, how they changed with withdrawal of the lithium. While this study has a number of methodological flaws, it is notable that the rate of relapse (52.4%) is similar to the 52.0% relapse found in the 1996 Reynolds augmentation discontinuation study (51).

There has been one report of the role of SGA augmentation of citalopram to prevent relapse (52). The report, which describes outcomes of a subset of 63 older participants from a large multicenter study, was conducted in three phases: 1) a prospective open-label trial of citalopram monotherapy to confirm treatment nonresponse; 2) adjunctive open-label risperidone therapy to identify responders; 3) double-blind continuation treatment with citalopram plus risperidone or citalopram plus placebo to assess relapse and safety. Despite an unconventional design selecting a study population with risperidone-responsive depressive symptoms, the authors found no statistically significant difference in rates of relapse. Thus, the data from this trial do not support the value of longer-term SGA augmentation as maintenance therapy.

In addition to the decision regarding initiation of augmentation, it is likely that geriatric psychiatrists will inherit patients already receiving combination or augmentation antidepressant pharmacotherapy, some of whom have hopefully achieved remission. In both the Reynolds et al. (51) and Fahy et al. (50) reports, slightly over 50% of those who had achieved remission with augmentation or combination pharmacotherapy suffered relapse following discontinuation. However, without an active versus placebo augmentation maintenance phase, it is not possible to know what role discontinuing the augmenting agent may have played in relapse. Unfortunately, if a patient has achieved remission with combination pharmacotherapy, there is insufficient evidence to weigh potential benefit of continuing current treatment versus risks of polypharmacy with ongoing pharmacotherapy.

Conclusions

To treat incomplete response in LLD, the practitioner is ultimately left with few evidence-based strategies and essentially no compelling longer-term data for adding medication to AD monotherapy. Further study should come in multiple realms. The first might be in randomized, placebo-controlled trials of augmentation or combination agents studied in younger populations such as lithium, triiodothyronine, buspirone, aripiprazole, and quetiapine as well as larger and longer studies of psychostimulants. Importantly, while SGAs as a class have been associated with an increased risk for sudden cardiac death in older patients as well as cerebrovascular adverse events in older patients with dementia (53), better understanding the risks associated with specific agents such as aripiprazole will be an important part of their evaluation in older adults. Study of combination therapy could also be informative, such as mirtazapine or bupropion in addition to an SSRI, as this strategy might entail a more benign side effect profile than expected from some of the augmenting agents such as lithium or SGAs. However, a large recent study in a mixed-age population did not demonstrate benefit from two AD combination strategies compared to SSRI monotherapy (54).

Despite the heterogeneous nature of late-life depression, very few of the reviewed studies report their data in a way that acknowledges the impact of factors such as medical illness or cognitive impairment. They vary in reporting whether a cognitive screen was utilized and, if so, what score was applied as an exclusion criteria. Of those that note a cognitive screen, all used the Mini-Mental Status Exam (MMSE) (55), with the lowest a mean of 26.4 (41). It is possible that mild cognitive impairment was present in many study participants, which could have moderated the effects of treatment, though this goes unaddressed. The reviewed studies also provide minimal information regarding the impact of medical comorbidity. The 2007 study by Dew et al. (40) did report that treatment to recovery is generally slower in those with higher medical burden, though not in those with cognitive impairment. In the Kok et al. study of lithium augmentation versus a switch to phenelzine (41), the lithium group had a higher burden of medical illness but was more likely to respond, while those on lithium who remitted did not differ from non-remitters in medical illness. It would be helpful if future

work on LLD would more explicitly address the effects of medical and cognitive features on response.

Funding for LLD trials is likely to be scarce and, in light of the call for more efficient services and interventions research (56), one further key area of investigation will likely emerge through comparative effectiveness research of psychotropic prescribing trends in older adults. It is likely that, in actual practice, a significant amount of addition to AD monotherapy is occurring despite the lack of an evidence base. It would be useful to characterize these patterns specifically in late-life depression, as some recent work has done in mixed-age populations (22, 57). In systems with access to pharmacy, symptom, and service data, these prescribing patterns can be linked to symptom burden or service utilization, as we have begun to do by pairing state-wide pharmaceutical claims with patient-level symptom and service data (58). In order to supplement data gathered in controlled trials, such approaches will be needed to generate evidence from prescribing as it occurs in the community.

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Agents for Partial Response

Table 1

Study	Quality of Evidence ^	N	Mean Age (y)	Diagnosis; mean MMSE	Initial agent; duration	Augmenting; duration	Measure	Findings	Comments
Kushnir, 1986 (33)	III	5	81	MDD, dysthymia; *	maprotiline, desipramine, trazodone; unclear	Lithium carbonate (0.15–0.4 mEq/L); unclear	Clinician assessment	5 (100%) improved	No adverse events (AEs) reported
Lafferman et al., 1988 (34)	III	14	73	13 unipolar, non-psychotic MDE; 1 BAD NOS; *	Maprotiline, amitriptyline, doxepin, trazodone; unclear	Lithium carbonate (0.7–1.3 mEq/L); unclear	Clinician assessment	7/14 (50%) “Complete improvement”; 3/14 (21%) “partial response”	Nausea and CNS side effects causing discontinuation in 4
Finch and Katona, 1989 (35)	III	9	76	ICD9 criteria for manic depressive psychosis or depressive neurosis, dementia excluded; *	TCA, with some patients also receiving carbamazepine or ECT during course; unclear	Lithium carbonate (0.43–0.86 mEq/L); n/a	Clinician assessment	7/9 (78%) with “good response”; 1/9 (11%) “intermediate”	2 (22%) patients with orthostatic hypotension and dizziness or tremor
van Marwijk et al., 1990 (36)	III	51	77	41 DSM-III unipolar; 9 BAD; 1 atypical; psychotic features in 29; *	TCA, TetraCA; 47 had 4wks of at least 75mg imipramine or cyclic equivalent	Lithium carbonate (0.4–0.8 mEq/L); unclear	Clinician assessment of “global clinical impressions”; Remission when pretreatment DSM-III symptoms vanished	18/51 (35%) responder; 15/51 (29%) partial 26/42 (62%) partial or complete response for unipolar No difference of response in those with evidence of cerebrovascular disease	6 (12%) patients with “symptoms and signs of neurotoxicity”; 4 (8%) patients developed hypothyroidism
Zimmer et al., 1991 (37)	III	15	74	11 DSM-III unipolar; 3 BAD; 27.4	Nortriptyline with plasma 50–150ng/ml; 4 weeks and HRSD>10	Lithium carbonate (0.3–1.0 mEq/L; mean 0.67); 3 weeks	HRSD-17 - response 10 - partial 11–17	3/15 (20%) responders; 7/15(47%) partial Responders had less medical illness	No AEs reported MMSE pre-and post-lithium significant improved (25.5 27.4, <i>p</i> <0.04)
Flint and Rifat, 1994 (38)	III	21	76	DSM-III-R unipolar, nonpsychotic; 28.3	nortriptyline (n=15, 77mg), fluoxetine (n=4, 35mg), or phenelzine (n=2, 53mg);6 weeks and HRSD 16	Lithium carbonate (0.5–1.0 mEq/L; mean 0.67) 2 weeks - HRSD24.6	HRSD-17 - response 8 - partial 9–15	5/21 (24%) responders; 3/21 (14%) partial No mention of response by medical diagnoses	10 (48%) developed dose-limiting side effects, including all 4 on SSRI.
Whyte et al., 2004 (39)	III	53	76	DSM-IV, unipolar, nonpsychotic, MMSE>15; 27.9	IPT + Paroxetine monotherapy (10–40mg/d), avg duration 10.7wk	Offered if little/no evidence of response or in case of relapse. - bupropion SR (50–450 mg/d) - lithium (goal 0.5–0.7 mEq/L) - nortriptyline (80–120ng/L)	HRSD-17 - response 10 × 3wks - partial recovery 11–14	Response by trial #: - 1:24/37 (65%) - 2:5/9 (56%) - 3:3/7 (43%) - total: 32/53 (60%)	Mean time to response after first augmentation: 6.0w/ks Bupropion SR associated with highest rate of discontinuation due to AEs (21/42, 50%)
Dew et al., 2007 (40)	III	69	76	DSM-IV, unipolar, nonpsychotic, MMSE>16; *	IPT + Paroxetine monotherapy (10–40mg/d), avg duration 12.9wk	Offered if little/no evidence of response or in case of relapse. - bupropion SR (50–400 mg/d) - lithium (goal 0.5–0.7 mEq/L) - nortriptyline (80–120ng/L)	HRSD-17 - response 10 × 3wks - partial recovery 11–14	Response by trial #: - 1:28/47 (60%) - 2:6/12 (50%) - 3:4/10 (40%) - total: 38/69 (55%) Slower recovery predicted by high general medical burden, not cognitive impairment	Over one-third of those eligible for augmentation did not receive it; many unwilling to accept or had medical conditions that precluded augmenting agents
Kok et al., 2007 (41)	II	29	73	DSM-IV, unipolar, psychosis not specifically excluded, MMSE> 14; 26.4	TCA or venlafaxine XR (150mg/d) 4 weeks	Randomized to either lithium augmentation (goal 0.6–1.2 mEq/L; mean 0.71) or	HRSD-17 - remission 10	Remission - Liaug: 5/15 (33%)	No subjects withdrawn due to AEs.

Study	Quality of Evidence [^]	N	Mean Age (y)	Diagnosis; mean MMSE	Initial agent; duration	Augmenting; duration	Measure	Findings	Comments
						phenelzine (max 60mg/d; mean 46mg/d) for 6 weeks	- response decrease 50% from baseline	- Switch to phenelzine: 0/14 (0%) Change on MADRS/HRSD: - Li: -13.1/-10.0 - phenelzine: +0.7/+0.1 Li group with higher mean medical comorbidities; remitters v. non did not differ significantly.	Tremors more common with Li; Memory impairment with phenelzine. Decrease in orthostatic hypotension
Rutherford et al., 2007 (43)	III	20	63	DSM-IV, unipolar, nonpsychotic; MMSE >24; 29.2	SSRI 6 weeks - fluoxetine 20mg/d - escitalopram 10–20mg/d - sertraline 100mg/d	Aripiprazole 5–15mg/d × 6wks	HRSD-24 - remission 10	10/20 (50%) met criteria for remission Change in HRSD: - remitters: 18.3 5.1 - non: 22.2 19.7 - all: 20.0 7.6 17/20 (85%) with “chronic medical issues”, no comment if modifies response	3 patients discontinued due to intolerable anxiety 9/20 (45%) had side effects of treatment, incl agitation, anxiety, drowsiness
Sheffrin et al., 2009 (44)	III	24	74	DSM-IV, unipolar, nonpsychotic; MMSE > 17; *	Escitalopram (20mg)for 16 weeks), followed by either duloxetine (120mg/d) or venlafaxine (225mg/d) for 12 weeks; Partial (11–15) or non-responders (>15) continued to augmentation	Aripiprazole 2.5–15mg/d (avg 9.0mg/d)for 12 weeks	HRSD-17 - no response ≥ 15 - partial 11–15 - remission 10 × 2wks	12/24 (50%) met criteria for remission HRSD 17.9 11.5, p<0.01 No comment on medical illness	3/24 (13%) dropped out due to failure to improve 2/24 (8%) discontinued due to side effects 1/24 (4%) significant increase lipids 0/24 (0%) significant increase glucose 6/24 (25%) gained >3kg

* Mean MMSE not provided

[^] Class I: randomized, controlled trials; Class II: well-designed observation studies with concurrent controls such as cohort or case-control; Class III: expert opinion, case series, case report, and studies with historical controls

Table 2

Agents for Acceleration

Study	Quality of Evidence [^]	N	Mean Age(y)	Diagnosis	Initial agent; duration	Augmenting; duration	Measure	Findings	Comments
Lavretsky and Kumar, 2001 (46)	III	10	79	9 DSM-IV unipolar, nonpsychotic; 1 depression secondary to Parkinson's Disease; *	Citalopram 8 weeks (mean 26mg); 0-3 weeks until MPH	MPH (mean 12.5mg)	HRSD-21 and CGI - response 10 and CGI 1 or 2 - "rapid" = response by day 14 - remission 10	4/10 (40%) patients with rapid response 6/10 (60%) achieved remission by week 8	3 (30%) reported side effects but no patient discontinued due to these
Lavretsky et al., 2003 (47)	III	11	78	DSM-IV unipolar, nonpsychotic; MMSE>23; *	Citalopram for 10 weeks (mean 27.5mg); augmentation started concurrently	MPH (mean 12.2mg); 8 weeks, then tapered off during last two weeks	HRSD-21 and CGI - response 10 and CGI 1 or 2 - "rapid" = response by day 14 - remission 6 - relapse >10 after MPH response achieved, maintained x 8wks	6/11 (55%) had rapid response by day 14 6/11 (55%) in remission by week 8 8/11 (73%) responders by week 8	5/8 (63%) responders maintained after d/c of MPH All reported 1-4 SEs, cited as reason for 1 drop out 2 required dose reduction of MPH due to nausea, anxiety No significant changes in weight, BP, HR
Lavretsky et al., 2006 (48)	I (pilot)	16	74	DSM-IV unipolar, nonpsychotic; MMSE>23; 28.0	Citalopram for 10 weeks (mean 33.3mg PBO group, 26.0 MPH group); augmentation started concurrently	10 randomized to MPH, 6 to PBO MPH (mean 15mg); 8 wks, then tapered off during last two weeks	HRSD-24 - response 10 - "rapid" = response by day 21 and maintained - remission 6 - relapse >10 x 2wks after response achieved, maintained x 8wks	Rapid Response: - MPH: 5/10 (50%) - PBO: 0/6 (0%) Remission by wk8: - MPH: 4/6 (67%) - PBO: 0/6 (0%)	4/10 in MPH group dropped out, 3 as a result of side effects

* Mean MMSE not provided

[^] Class I: randomized, controlled trials; Class II: well-designed observation studies with concurrent controls such as cohort or case-control; Class III: expert opinion, case series, case report, and studies with historical controls

Table 3

Maintenance of Augmentation Medications following Remission

Study	Class [^]	N	Mean Age (y)	Diagnosis	Initial agents; duration	Aug/Comb agent (n)	Measure	Findings	Comments
Reynolds et al., 1996 (51)	II	39	62	DSM-IV, unipolar, nonpsychotic, no dementia; *	Ongoing trial of maint for LL.D; received adjunctive medication if HRSD-17 >10 after 8wks nortriptyline at 80–120 ng/mL	- Li (0.5–0.8 meq/L) (16) - perphen (4mg/d) (8) - Li + perphen (12) - Li parox (2) - parox alone (1)	HRSD-17 - Response 10 × 3wks - Relapse reappearance HRSD 17	Acute-phase responders: - 25/39 (64.1%) aug - 99/119 (83.2%) non-aug Cont-phase relapsers: - 13/25 (52.0%) aug relapse response, - 6/99 (6.1%) non-aug relapse	Comparing Li to perphenazine, no difference in rate of response, relapse, or sustained remission
Hardy et al., 1997 (49)	I	12	76	DSM-III-R unipolar w/o depressive symptoms 1y on Li aug; *	Responders to Li augmentation after 6mos TCA monotherapy and symptom-free for 1y while being maintained on Li augmentation	Lithium withdrawn from half at rate < 150mg/d/wk in double-blind, PBO-controlled fashion (level 0.4 mEq/L)	Recurrence: - hospitalization - change AD dose/type - MADRS > 15 and/or +10 from baseline - GDRS > 20	- 2/4 on Li had recurrence, both after significant stressors (spouse death, CVA causing dementia) - 2/5 on placebo had recurrence with long delay in response to Li re-initiation (7-week and 92-week)	- placebo group w/fewer side effects (esp urinary symptoms, neurotoxicity)
Fahy et al., 2001 (50)	III	21	78	Unipolar MDE “deemed to be clinically well”; *	AD class not specified Time “well” not defined	Lithium tapered over 2–12 weeks Did not include: - patients known to have relapsed in the past not included;	Relapse “a re-emergence of depressive symptoms at any time”	11/21 (52.4%) relapsed - relapsers had been on Li longer (2.5y v. 1.4, p=0.007) - no clear predictors of relapse	- 11/21 relapsed (52.4%) - relapsers had been on Li longer (2.5y v. 1.4, p=0.007) - no clear predictors of relapse
Alexopoulos et al., 2008 (52)	II	63	63	DSM-IV, unipolar, +/- psychosis, MMSE > 23; *	Citalopram monotherapy (20–40mg/d) × 4–6 wks; continued to augmentation only if <50% rdxn HRSD	Phase 2: C (avg 40.0mg/d) + risperidone (0.25–1mg/d, avg 0.8mg/d) × 4–6wks; Phase 3: Those who met criteria for remission then continued on C+R or C +PBO (dbl-blind)	Remission: - HRSD-17 7 - CGI 1 or 2 Relapse: - CGI 6 or 7 - HRSD 16 - discontinuation - deliberate self-injury or suicidal intent	Time to and rate of Relapse: - R: 105d, 18/32 (56%) - PBO: 57d, 20/31 (65%) - p for time to relapse 0.069	

* Mean MMSE not provided

[^] Class I: randomized, controlled trials; Class II: well-designed observation studies with concurrent controls such as cohort or case-control; Class III: expert opinion, case series, case report, and studies with historical controls