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Risk of Adverse Events with the Use of Augmentation Therapy for the Treatment of Resistant Depression

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Abstract

Augmentation therapy is used for those situations where a patient's depression is either treatment-resistant, or partially and/or insufficiently responsive to treatment. It also may be used to attempt to induce a more rapid treatment response.

Using drugs together may increase the risk of adverse effects, through potentiation of existing adverse effects or alterations in plasma concentrations of the drug. It is important that clinicians are aware of potential risks of augmentation therapy.

Lithium augmentation of a tricyclic antidepressant is relatively well tolerated and the dangers are no greater than using these medications on their own. There are also no reports of serious adverse events when lithium is added to a monoamine oxidase inhibitor. With lithium augmentation of selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitor (SSRI) therapy there have been case reports of the development of a central serotonin syndrome, and thus caution must exercised.

A serious concern when using a tricyclic antidepressant to augment an SSRI is the effect of the SSRI on the cytochrome P450 system and the resulting significant increase in tricyclic antidepressant blood concentrations.

Augmentation with thyroid hormones appears to be well tolerated and effective. Case reports and open studies indicate that augmentation with buspirone and the psychostimulants, carbamazepine and valproic acid (valproate sodium) is effective and results in minimal adverse effects. However, there is no empirical

evidence supporting these results. Recent work supports the tolerability and efficacy of pindolol augmentation.

Considerable caution should be exercised when combining psychotropic drugs. The practitioner should only do so with a full knowledge of the compounds involved and their pharmacological properties.

The addition of a second agent to an existing antidepressant regimen, with the aim of achieving an improved clinical response, is referred to as augmentation therapy. This should be distinguished from combination therapy where 2 or more medications are used together to effect a synergistic response and adjunctive therapy where a second agent is added to reduce associated symptoms such as anxiety or insomnia. Augmentation therapy is considered for those situations where depression is either treatment-resistant, or partially and/or insufficiently, responsive to treatment. It may also occur in an attempt to accelerate treatment response.

Augmenting antidepressant response has proven to be an increasingly popular clinical strategy and there are now claims for many drugs to have such an effect. The principle reason for the rise in augmentation therapy is the continuing failure of existing antidepressant treatments to successfully treat all depressed patients. Between 10 and 30% of depressed patients are classified as treatment-resistant and another 12 to 15% are only partial responders to adequate therapy.[1-3]

The clinical effect of augmentation may be through a synergistic effect or via different neurotransmitter and second messenger systems. The actual mechanisms of action are not known but are hypothesised with varying amounts of evidence. However, combinations of drugs may also increase the risk of adverse effects, either through interference with the efficacy of the primary drug, potentiation of existing adverse effects, or large alterations in plasma concentrations of either drug. It is important that clinicians are aware of potential risks of augmentation therapy.

This review critically assesses current scientific evidence pertaining to the tolerabilities of augmentation therapies. A large proportion of current data supporting a variety of augmentation strategies is either anecdotal or derived from case reports. There are few controlled studies; hence, data regarding drug tolerability as well as response are scarce, and the frequency of adverse effects cannot be calculated. Data from controlled studies, where available, have been emphasised.

1. Lithium Augmentation

The most intensively studied augmentation strategy is the addition of lithium to currently existing tricyclic antidepressant therapy. Studies, both open and controlled, have demonstrated consistent and significant responses to lithium augmentation of antidepressant treatment.[4-7] The dosage of lithium carbonate used has usually been between 500 to 1200 mg/day, subsequently adjusted to achieve adequate plasma lithium concentrations if considered necessary.

Published data concerning lithium augmentation of monoamine oxidase inhibitor (MAOI) therapy are limited. There are no placebo-controlled studies, although clinical perception through open trials and case reports is of similar response rates to the tricyclic antidepressants.[8,9]

Serious adverse reactions have been reported rarely in the extensive investigation of lithium augmentation of tricyclic antidepressants. Adverse effects are those that would be expected with the individual drugs – the anticholinergic and cardiovascular adverse effects of the tricyclic antidepressants, and nausea, diarrhoea, abdominal pain, muscle weakness and fine tremor with lithium. To date, there have been reports of mood elevation after the addition of lithium to a cyclic antidepressant in 6 patients: 2 (in a study of 9) with a history of bipolar disorder;[10] 2 patients with unipolar disorder who experienced a hypomanic episode when on the tricyclic antidepressant alone;[11] a patient with a history of psychosis and bipolar disorder;[12] and 1

patient (unipolar/bipolar not specified) in a study of 51 elderly people.[13] The plasma concentrations of the tricyclic antidepressants were not reported. Mood elevation has also been seen following discontinuation of lithium augmentation of desipramine and nortriptyline.[14] We can therefore conclude that lithium augmentation is relatively well tolerated and the dangers are no greater than using these medications on their own.

There are also no reports of serious adverse events when lithium has been added to MAOI therapy. There is no indication that the risks of hypertensive crises are greater when lithium is added.

Response to lithium augmentation of selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitor (SSRI) therapy in case reports and open treatment trials has been reported by a number of groups.[15-18] In 1 of 2 published, double-blind, placebo-controlled trials of lithium augmentation of SSRIs, lithium was found to be superior to placebo in 62 patients: there were no withdrawals in the fluoxetine-lithium group due to adverse effects.[19] This positive finding was replicated by the second study using citalopram in 69 patients: the authors reported no evidence of accentuation or aggravation of adverse events.[20]

With lithium augmentation of SSRIs there are reports of occasional but significant complications involving a central serotonin syndrome, i.e. a toxic serotonergic hypersensitivity, marked by confusion, restlessness, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, hypomania, diarrhoea and possibly death.[21-23] There are 2 reported cases of lithium augmentation inducing mania or hypomania.[24] One case of absence seizures,[25] and 1 of delirium[26] have also been reported. These reactions have occurred both with therapeutic plasma concentrations and when plasma lithium has risen to toxic concentrations (without physical symptoms) with fluoxetine. Clinicians must be mindful that, although a serotonin syndrome is rare and the risks with the other SSRIs and venlafaxine and nefazodone may not be comparable to that of fluoxetine, any combination of drugs which together increase serotonin neurotransmission via different mechanisms of action theoretically has the potential to cause a serotonin syndrome.[23]

CNS adverse effects occur more frequently in elderly patients using lithium (tremor and delirium). In addition, renal as well as thyroid abnormalities and dose-limiting adverse effects (neuromuscular or neurological) have been reported when lithium carbonate was added to existing antidepressant treatment in elderly participants, even at therapeutic concentrations of lithium.[13,27] In 1 of these studies, 50% of patients experienced adverse effects, and they were older than those not experiencing adverse effects.[27] In the other study, 11% of patients experienced neurotoxicity.[13] There appears to be a risk of recurrence of depression and subsequent lithium resistance in the elderly when lithium augmentation is discontinued.[28]

Studies that have shown positive effects of lithium augmentation have generally achieved plasma concentrations of lithium within the normal range (0.4 to 1 mmol/L). However, there appears to be no correlation of response to lithium concentrations:[5,6,18,29] there are reports of a small number of patients responding to lower concentrations of lithium, such as 0.3 and 0.54 mmol/L.[5,17,18,27] de Montigny[30] suggests there may be a plateau effect and titrating concentrations up may only increase the risk of adverse effects.

The site of pharmacological response produced by lithium augmentation remains unclear, mainly because of the multiple effects of lithium. Lithium carbonate has been shown not to modify antidepressant plasma concentrations.[5,29,31,32] It is postulated that the rapid response to lithium augmentation is due to presynaptic serotonergic enhancement of antidepressant-induced sensitisation of postsynaptic serotonin receptors.[5] Other neurotransmitter systems, particularly noradrenergic transmission and second messenger systems have also been implicated.[6,33-36]

2. Thyroid Hormone Augmentation

Tri-iodothyronine (T_3) added to imipramine was found to enhance and accelerate recovery in

patients described as experiencing retarded depression.[37] As cited in a review of thyroid hormones in the treatment of affective disorders, a number of studies replicated this work, most of them substantiating it.[38] Other studies have yielded mixed results: some have found a lack of efficacy of T_3,[39,40] 1 suggested particular efficacy in subclinical hypothyroidism[41] and another indicated that T_3 was equally effective as lithium.[42]

Plasma concentrations of tricyclic antidepressants are not altered by T_3.[38,43] Desipramine was found to have no significant effect on thyroid indices.[44,45] Therapeutic dosages of T_3 (25 to 50 μg/day) or thyroxine (T_4) (100 μg/day) appear well tolerated with standard doses of tricyclic antidepressants.[38] The combination does not increase the adverse effects of either drug or cause additive effects; the most common adverse effects reported have been drowsiness, dizziness, dry mouth, tremor, anxiety, agitation and insomnia, but are usually mild or absent.[37,38,46] Cardiotoxicity, known to be an effect of both thyroid hormones and tricyclic antidepressants, has not been reported with T_3 or T_4 augmentation.[38,43] However, caution is advised in prescribing thyroid hormones for elderly patients or those with cardiac insufficiency.[46]

There is a paucity of controlled studies of MAOIs and thyroid hormones. A single case study reported clinical improvement when T_3 was added to phenelzine with no significant adverse effects.[47] MAOIs and thyroid hormones affect the adrenergic system, but no adverse effects are found in the literature.[38]

Case studies of T_3 augmentation of fluoxetine suggest it may be effective.[48,49] Double-blind studies are still required with each of the SSRIs before any conclusions can be drawn regarding tolerability or efficacy.

A number of hypotheses regarding the mechanisms underlying thyroid hormone potentiation of tricyclic antidepressants have been postulated as follows:

- in patients who are euthyroid, the addition of T_3 may bring them to a previously not attained optimal state[43]
- T_3 enhances receptor response synergistically with increased neurotransmitter concentrations induced by the antidepressant[37]
- there is evidence that thyroid hormones enhance central ß-adrenergic receptor function.[50]

No consistent effect on adrenergic receptor number and function has been demonstrated, but this does not exclude the possible potentiation of adrenergic receptors by T_3.[51]

The evidence to date of the tolerability and efficacy of thyroid hormone augmentation of antidepressant treatment is encouraging. Routine monitoring of thyroid indices and low dosages (25 to 50 μg/day) of T_3 augmentation in euthyroid patients for 2 to 3 weeks are recommended. Such an approach reduces the risk of inducing hypothyroidism via a negative feedback effect on the thyroid axis.[1] Others advocate maintaining the T_3 for longer periods, including continuing for 60 days if the depression responds.[52] Long term studies are not available.

3. Tricyclic Augmentation of Specific Serotonin Reuptake Inhibitors

Tricyclic augmentation of SSRIs has become a popular approach amongst clinicians despite limited research. The catalyst was a finding of an improvement in 87% of patients when fluoxetine was added to ongoing non–MAOI antidepressant treatment in a retrospective study.[53] This was substantiated in the open addition of a tricyclic antidepressant to fluoxetine[54] and a combination of nortriptyline and either sertraline or fluoxetine, with or without concurrent lithium.[55] No adverse effects were reported in these studies. Low doses of tricyclic antidepressants were used because of the possibility of elevation of serum tricyclic antidepressant concentrations and subsequent toxicity. However, in another study, of 12 patients taking a combination of fluoxetine and desipramine, 2 were removed from study because of adverse effects: ag-

itation, blurred vision, panic attacks and micropsia.[16]

In a single case report, a 60% increase in steady-state desipramine concentrations was measured after the addition of sertraline 50 mg/day.[56] The patient experienced no adverse effects and felt more motivated than on previous successful therapy.

A serious concern with using a tricyclic antidepressant to augment an SSRI is the effect of the SSRI on the cytochrome P450 (CYP) isoenzyme system and the resulting significant increase in tricyclic antidepressant blood concentrations. All SSRIs potentially inhibit the CYP2D6 isoenzyme, and thus the metabolism of other drugs, including tricyclic antidepressants, which are cleared by this system. The SSRIs differ in their effects on specific CYP enzymes. Paroxetine and fluoxetine are potent inhibitors of CYP2D6, whereas sertraline, citalopram and fluoxetine have a weaker effect (and nefazodone and venlafaxine weaker still).[57]

Coadministration of SSRIs and tricyclic antidepressants can lead to potentially toxic plasma concentrations of the tricyclic antidepressant with significant clinical consequences, such as delirium and grand mal seizures,[58] and psychomotor retardation, decreased energy and drowsiness.[59] Weilburg et al.[54] reported that toxic plasma tricyclic antidepressant concentrations were not observed in patients taking low doses of tricyclic antidepressants, although the plasma concentrations were higher than expected. They did however recommend initiation of tricyclic antidepressant augmentation (desipramine or nortriptyline) at low dosages (25 to 50 mg/day), with plasma monitoring.

These cases have all been with fluoxetine and it is likely that those SSRIs with weaker inhibition of CYP2D6 will not raise tricyclic antidepressant concentrations to the degree that fluoxetine does.[60] There is also the potential for drug-drug interactions with other CYP isoenzymes. For example, nefazodone and fluvoxamine are potent inhibitors of CYP3A4 and fluvoxamine also of CYP1A2; the other SSRIs have moderate to minimal effects and venlafaxine has minimal effects on these 2 systems.[57,60,61]

The reported enhancement of antidepressant response by SSRI and tricyclic antidepressant augmentation of TCA and SSRI therapy, respectively, may be due to an interaction between the serotonergic and adrenergic systems. There may be a synergistic effect of acceleration of ß-adrenoceptor down-regulation and enhancement of serotonergic activity.[55,62,63] Elevated plasma tricyclic antidepressant concentrations were not considered to be causal in effect by these investigators

4. Pindolol Augmentation

Interest has been generated recently by reports of rapid potentiation of the SSRI antidepressant effect when pindolol has been added to therapy. Based on preclinical evidence that blocking 5-HT_{1A} somatodendritic receptors might augment the efficacy of serotonin uptake blockers, Artigas and colleagues[64] augmented SSRI or MAOI treatment with pindolol, a ß-blocker which shows strong antagonist activity at 5-HT_{1A} receptors. In their open study, 7.5mg pindolol daily was added to a regimen of paroxetine, phenelzine, fluvoxamine or imipramine. The results showed a rapid, full recovery in 5 of 8 patients whose mood disorder had shown a partial or no response previously.

Further studies of concurrent treatment substantiated these results.[65,66] However, patients taking sertraline in 1 study did not show the same response.[65] It was postulated that as sertraline has a lesser affinity for the CYP2D6 isoenzymes than do fluoxetine and paroxetine, plasma concentrations of pindolol may have been lower in this group. Two double-blind, placebo controlled, studies of fluoxetine plus pindolol found neither any difference in the rate of response between the groups[67] nor in differences in average time to remission and overall disease response between groups.[68]

The investigators have noted that the general tolerability of these combinations was good, although 1 patient (of 9 taking paroxetine in a total of 19 taking SSRIs plus pindolol) became manic.[65] In a double-blind placebo controlled study with fluoxetine, adverse events were reported in 9.1% of patients, mainly nausea and di-

arrhoea; heart rate reduction was between 3 to 8 beats/min and there was no change in blood pressure.[66]

The most recent studies in this area have reported positive results with combinations (not augmentation) of pindolol and paroxetine,[69] fluoxetine,[70] buspirone and fluvoxamine,[71] and nefazodone.[72] Two placebo-controlled studies of pindolol with paroxetine and with fluoxetine, reported no differences in the incidence or severity of adverse effects between active and placebo groups. A small number of participants were withdrawn due to adverse effects: 2 of 40 in each of the active and the placebo groups in the paroxetine study; 5 of 56 taking pindolol plus fluoxetine; and 1 of 56 in the comparison placebo group in the second study.[69,70] Nausea, diarrhoea and headache were the most common adverse effects and tended to be transient.[69]

The SSRIs are believed to desensitise 5-HT_{1A} autoreceptors which control cell firing and terminal serotonin release by a negative feedback mechanism.[64] Tolerance develops, which pindolol may hasten and increase by blocking 5-HT_{1A} autoreceptors and preventing the inhibitory action.[64] This hypothesis is still under discussion. β-Blockers have been implicated in causing depression and, while a recent review of the literature indicates there is inadequate evidence to support this, the authors also believe it cannot be discounted.[73] The benefits of pindolol augmentation, its tolerability and any mechanism of action are still to be elucidated.

5. Carbamazepine and Valproic Acid (Valproate Sodium) Augmentation

The usefulness of the addition of the mood stabilisers carbamazepine and valproic acid (valproate sodium) to antidepressant therapy has not been well studied and there are no controlled studies to support these combinations. Case reports indicate marked improvement after the addition of carbamazepine to clomipramine[74] and valproic acid to fluoxetine or fluvoxamine (both in elderly patients).[75] The addition of phenelzine or tranylcypromine to carbamazepine, with or without lithium, resulted in substantial improvement in 4 of 10 patients, despite having failed to respond to the same MAOI without carbamazepine previously.[76]

The literature suggests caution when using either carbamazepine or valproic acid in combination with a tricyclic antidepressant with regard to pharmacokinetic interactions.[32,76,77] Carbamazepine is a potent enzyme inducer whereas valproic acid is an enzyme inhibitor. The former lowers tricyclic antidepressant concentrations and the latter probably raises antidepressant concentrations.[32] Carbamazepine may increase hydroxy-tricyclic antidepressant metabolites and thus may be cardiotoxic.[77]

6. Augmentation with the Psychostimulants

Methylphenidate has been reported to be useful in refractory depression, although there have been no controlled studies.[32] A small early study described the successful addition of methylphenidate 20mg to imipramine in psychotic depression. Methylphenidate increased plasma tricyclic antidepressant concentrations and the authors hypothesised a mechanism of action involving enzymatic inhibition by methylphenidate.[78]

A retrospective study showed 1 of 5 patients' depression responded when methylphenidate or dextroamphetamine was added to MAOIs alone, and 5 of 8 patients' depression responded when added methylphenidate or dextroamphetamine was to a combination of MAOI and tricyclic antidepressants.[79] The most frequent adverse effect was orthostatic hypotension. In a complex study of the effects of the addition of a stimulant, either dextroamphetamine or pemoline, to an MAOI, 25 (78%) of 32 patients' condition responded for at least 6 months, with 31% of patients reporting a maintained improvement. No hypertensive crises were reported, although the authors warned of the need to take precautions in using this combination.[80]

An open trial of methylphenidate augmentation of paroxetine and fluoxetine proved to be efficacious, rapid and well tolerated.[81] The investiga-

tors noted that the improvement could be due to increased plasma concentrations of the SSRIs, treatment of unrecognised asthenia or even a placebo effect. Methylphenidate has a number of neurochemical actions, including influencing dopaminergic and noradrenergic transmission.

Methylphenidate elevates mood by releasing catecholamines and blocking their reuptake. Stimulants may increase blood concentrations of other drugs and risk hypertensive crises in combination with MAOIs. However, data are not available or are limited on drug interactions. The adverse effects of these stimulants, including hypertensive and hyperthermic crises[79] and the risks of abuse and dependence potential and withdrawal reactions are an additional consideration, particularly in combination with other antidepressants.[46]

7. Buspirone

Open studies suggest buspirone augmentation of SSRIs may be useful in treatment-resistant depression, but again the data are limited. A full or partial recovery was demonstrated after the open addition of buspirone to fluoxetine,[82,83] to fluoxetine or fluvoxamine,[84] and to trazodone in 2 geriatric patients.[85] The adverse effects in these trials were reported to be minimal and included dizziness, nervousness, restlessness, nausea and headache.[86] However, buspirone has been reported to induce mania,[86] euphoria[85] and a serotonin syndrome after ingestion of higher than prescribed doses of citalopram and buspirone.[87]

Buspirone is a partial 5-HT_{1A} agonist and with an SSRI would enhance serotonin transmission at several points.[84] This could potentiate SSRI adverse effects such as apathy or sexual dysfunction. Howland[88] has proposed a possible role for the buspirone metabolite 1-(2-pyrimidinyl)-piperazine, which is an α_2-adrenergic antagonist enhancing the release of noradrenaline.

8. Discussion

Most of the evidence supporting augmentation agents is anecdotal and in the form of case reports. Few well performed double-blind placebo controlled studies of augmentation therapy have been carried out to determine tolerability as well as efficacy. There is a body of scientific evidence supporting lithium and T_3 as well tolerated and effective augmentation agents.

Case reports and open studies indicate augmentation with buspirone, carbamazepine, valproic acid, methylphenidate and amphetamine may be effective and cause minimal adverse effects. However, there is no empirical evidence supporting this. There is also no empirical evidence for the tolerability and efficacy of the addition of a tricyclic to an SSRI. Recent work is finding evidence supporting a role for pindolol combination with regard to tolerability and efficacy.[69-71]

Because of possible complex pharmacodynamic and pharmacokinetic interactions, augmentation therapy is not without its potential complications, although reports have been relatively uncommon. Lithium toxicity and the serotonergic syndrome have been reported to occur when lithium has been added to an SSRI. It is therefore advisable to add lithium to an SSRI with caution, commencing with low doses and careful monitoring of serum concentrations and clinical state of the patient. Lithium augmentation requires the usual follow-up testing of plasma concentrations every 3 or 4 months, and yearly checks of thyroid and renal function.

An SSRI and tricyclic antidepressant combination can result in toxic concentrations of the tricyclic and there are several reports of serious complications, such as delirium and convulsions. Close plasma monitoring of the tricyclic together with administration of low doses of tricyclic antidepressants is essential if this strategy is embarked upon. Electrocardiographic monitoring is also advised as tricyclic toxicity will result in cardiac abnormalities.

Data are not available to indicate whether adverse effects are related to faster rather than slower augmentation. Augmentation agents tend to be initiated at relatively low doses. The potential for drug-drug interactions occurs when a new drug is initiated, when the dose of any drug is altered, or

when a drug is ceased. Adverse events that have been reported have appeared anytime from between a couple of days and a few weeks, sometimes months, after initiation of the augmentation therapy; however, they have not always been documented.

There is evidence that there are neither differences between men and women in the development of adverse events, nor between unipolar and unipolar patients; however, adverse effects may limit the usefulness of some augmentation strategies in the elderly.[89] There is an even greater paucity of work in augmentation therapy in geriatric patients (who are considered to be at greater risk of interactions) than in younger age groups, so it is not possible to make any firm conclusions, but caution is advisable.

Unfortunately, the topic of augmentation therapy is permeated with more mythology than scientific data. Considerable caution should be exercised when considering embarking upon psychotropic drug combinations, and it should be done with the full knowledge of the compounds involved and their pharmacological properties. The clinician should also avoid 'researching' the effects of drug combinations on his patients in the clinical setting and should apply well established and proven approaches which are known to be relatively well tolerated.

If an augmentation strategy which is not well established for efficacy and/or tolerability is used, informed consent should be obtained from the patient after discussing risks, benefits and possible adverse effects of this strategy. When appropriate, clinicians should obtain a second opinion from a senior colleague. Such procedures can also be monitored more easily if in-patients are involved.

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