AMISULPRIDE AS AN AUGMENTATION AGENT IN TREATMENT RESISTANT DEPRESSION: A CASE SERIES AND REVIEW OF THE LITERATURE

Hans Rittmannsberger

Department of Psychiatry, General Hospital Steyr, Steyr, Austria
Department of Psychiatry 1, Kepler University Hospital, Linz, Austria

SUMMARY

Amisulpride (AMS) in low dosage has been used effectively for treatment of dysthymia. Yet there is a dearth of reports on its use as an augmentation agent in therapy-resistant depression. We deal with this issue presenting case reports and a review of the literature. The addition of 50 mg amisulpride (AMS) to antidepressant therapy in seven patients with depression at different stages of treatment resistance, one of them a case of recurrent brief depression, is described in this report. Augmentation with AMS led to a profound improvement in psychopathology in most patients. The only side effects were elevation of prolactin levels and occasional weight gain. In most cases, improvement occurred early, after only 1-2 weeks of treatment. In some patients, reduction or cessation of AMS led to an immediate and intense recurrence of depressive symptoms that resembled a withdrawal syndrome. Further investigations into the clinical utility and the mode of action of AMS as an augmentation agent are warranted.

Key words: *amisulpride – depression - treatment resistant – augmentation - withdrawal syndrome*

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INTRODUCTION

Amisulpride (AMS) is a selective antagonist to D2 and D3 dopaminergic receptors. In contrast to other antipsychotics, its affinity for D3 receptors is equal to or even greater than its affinity for D2 receptors (Noble & Benfield 1999). AMS preferentially binds to limbic rather than nigrostriatal structures (referred to as "limbic selectivity"), an effect that is likely mediated by the high density of D3 receptors in the limbic system (Schoemaker et al. 1997). Low doses of AMS exert their effect only at presynaptic D2 autoreceptors, which control the synthesis and release of dopamine and thus increase dopamine availability, especially in the nucleus accumbens (Perrault et al. 1997, Schoemaker et al. 1997). The latter effect is the rationale for the use of low doses of AMS in the treatment of the negative symptoms of schizophrenia (50–300 mg) and of dysthymia (25-100 mg).

In all, there have been eight randomized controlled trials (RCTs) that showed the efficacy and tolerability of low-dose AMS for the treatment of dysthymia and, to a lesser extent, depression. In these studies, treatment with AMS was compared to treatment with amitriptyline (Ravizza 1999), amineptine and placebo (Boyer et al. 1999), fluoxetine (Jori et al. 1998, Smeraldi 1998), imipramine and placebo (Lecrubier et al. 1997), paroxetine (Cassano & Jori 2002), sertraline (Amore et al. 2001), acetyl-L-cysteine (Zanardi & Smeraldi 2006), or placebo only (Costa-e-Silva 1990). Although the effects of AMS on dysthymia are well documented (De Lima et al. 1999, Komossa et al. 2010, Noble & Benfield 1999, Racagni et al. 2004), its use as a treatment is rather modest, which is likely due to the fact that it is licensed for this indication only in some European countries (e.g., Czech Republic, Italy, and Portugal).

There are very few reports in the literature on the use of AMS as an augmentation agent for depression. Recent reviews on the use of second-generation antipsychotics (SGAs) as augmentation treatments for therapy-resistant depression (Kato & Chang 2013, Nelson & Papakostas 2009, Shelton & Papakostas 2008) do not include AMS as a possibility. Nevertheless, in some countries, such as the Czech Republic, AMS augmentation seems to be quite common (Ceskova et al. 2011). In Austria, AMS is licensed only for use in the treatment of schizophrenia. We have some experience, however, with the use of AMS as an off-label augmentation agent for patients with difficult-to-treat depression. In this paper, we illustrate these experiences and provide a review of the available literature describing the use of AMS for this indication.

METHODS

All patients were initially treated as inpatients in Psychiatric Department 1 of Kepler University Hospital. Ambulatory treatment was provided by the outpatient clinic or in the author's private practice. All patients presented with some form of treatment resistance. The stages of resistance were defined according to the operational criteria provided by Souery et al. (1999). Non-response to one adequate antidepressant trial corresponds to stage A (non-responder). Non-response to two or more antidepressant trials corresponds to stage B (treatment resistant depression - TRD) and can be subdivided according to treatment duration from TRD 1 (12–16 weeks) to TRD 5 (36–52 weeks). Non-response

to several treatments over more than 1 year corresponds to stage C (chronic resistant depression - CRD). For clinical ratings, the Clinical Global Impressions Scale (CGI) (Guy 1976) was used. The clinical data of the patients are summarized in Table 1. Given that the use of AMS for depression is off-label in Austria, all patients were required to provide informed consent to be treated with AMS.

CASE REPORTS

Patient 1 (female)

This patient had been previously treated for depression unsuccessfully in two other clinics. At the time that she was admitted to our clinic, she was severely depressed, feeling paralyzed, highly anxious, and hopeless about her health and the future. She was unable to perform housework, feared that she would develop dementia, stayed in bed for most of the day, and ruminated about financial problems that she perceived as an existential threat.

A course of electroconvulsive therapy (ECT) was proposed to her, but she refused. We started treatment with amitriptyline and lithium. After 4 weeks of treatment, her condition had only minimally improved. As such, 50 mg of AMS was added to the treatment regimen. After 5 days, the patient became more active and, 2 days afterward, admitted to feeling better for the first time. Ten days after the start of AMS, there was an obvious and considerable improvement in her mood and drive, and she reported that she felt joyous again. The patient was discharged 19 days after initiation of AMS treatment.

Patient 2 (female)

For 8 months, this patient had been severely depressed with complaints of fatigue and a lack of joy, interest, and appetite. She had unintentionally lost 10 kg of weight in 3 months and was unable to perform her housework. Suicidal ideation was present.

The patient's treatment regimen was changed from escitalopram to mirtazapine, which resulted in moderate improvement. After 3 weeks, she was discharged with partially remitted depression on a regimen of 30 mg mirtazapine and 1.5 mg bromazepam. At an outpatient visit 10 weeks after the initiation of mirtazapine, the patient reported a recurrence of depression upon ceasing intake of bromazepam the previous fortnight. She was agitated, anxious, and awoke early in the morning. A dose of 50 mg AMS was added to her regimen and, at her next appointment, she was in a good mood and was free of depressive symptoms. The patient reported that she felt better just a few days after starting AMS and that she was completely well 2 weeks after the initiation of the AMS treatment. As possible side effects, she reported an increased appetite and a weight gain of 3 kg.

Patient 3 (female)

This patient was receiving a disability pension since young age due to recurrent depressive episodes and bulimia. She suffered from frequent bulimic attacks and was considerably underweight (BMI 16.7). Over a 16-month period of depression, the patient had undergone four hospitalizations and had received two courses of ECT without reaching stable remission. Besides her severely depressed mood, she was agitated and highly anxious with massive rumination and a permanent desire to ask for advice. A dose of 50 mg AMS was then added to a regimen of escitalopram, pregabalin, and quetiapine. In the second week, the patient began to feel better and, at the end of the second week, she felt better than she had for years.

Six weeks after starting AMS, the patient reported galactorrhea. When measured, prolactin (PRL) levels were 154.2 ng/ml (normal range: 1−25 ng/ml). Treatment with 0.25 mg cabergoline did not improve PRL levels, and thus, after an additional 4 weeks, AMS was tapered and withdrawn over 2 weeks. The patient's mood deteriorated in the days following cessation of AMS. In the second week after stopping AMS, the patient fell into a severe depressive state with feelings of despair, continuous rumination, and difficulties in making decisions and remained this way for many weeks. Bulimic attacks were present over the entire period with a frequency of approximately 2 attacks per week, with a tendency to occur more frequently when mood deteriorated.

Patient 4 (female)

Stressful life events had led this patient to a state of complete exhaustion. She was depressed, complained about a complete loss of energy, yet was agitated and fearful. Treatment was initially started with sertraline and trazodone. As progress was slow, 50 mg AMS was added after 4 weeks as augmentation therapy. Although the addition of AMS further improved her state, she still experienced a lack of energy. Hence, 150 mg bupropion was added to her treatment regimen. The patient was able to be discharged after 8 weeks, but was not free of symptoms, as she still experienced low energy and a reduced ability to cope with stress. As an outpatient, bupropion was increased to a dose of 300 mg, which led to complete recovery approximately 4 months after the start of treatment.

Five months later, the patient reported amenorrhea and galactorrhea. AMS treatment was discontinued, as it was considered most likely to have caused these side effects. Moreover, its effectiveness in this patient was doubtful. Approximately 1 week after discontinuing AMS, her mood worsened to such an extent that she decided to resume treatment with AMS. Within a week of restarting AMS, the patient's mood improved.

Table 1. Data from seven patients undergoing augmentation treatment with AMS. Only treatments with duration of at least 4 weeks are reported (numbers in treatment columns reflect consecutive treatment episodes; actual medication: the medication to which AMS was added)

No	Sex	Age		Duration of current episode	Treatment(s) for current episode		Staging for treatment resistance*	Start AMS	CGI Discharge/next appointment (time since start)
					Prior treatment(s)	Actual medication			
1	F	65	F33.2	8 months	1. Escitalopram 20mg, trazodone 100mg 2. Mirtazapine 30mg 3. Bupropion 300mg, ziprasidone 160mg, thyroxine 50mcg	4. Amitriptyline 150mg, lithium carbonate 450mg	B (TRD4)	7	2 (19 days)
2	F	64	F33.2	3 months	1. Escitalopram 10mg	2. Mirtazapine 30mg	B (TRD1)	6	1 (4 weeks)
3	F	35	F33.2 F50.2	16 months	1. Paroxetine 100mg 2. ECT 3. Amitriptyline 100mg, olanzapine 5mg 4. ECT	5. Escitalopram 20mg, pregabalin 300mg, quetiapine 300mg	C	7	1 (4 weeks)
4	F	39	F32.1	2 months		1. Sertraline 75mg, trazodone 100mg	A	6	3 (4 weeks)
5	F	57	F33.2	9 months	1. Duloxetine 120 mg, trazodone 150mg 2. Mirtazapine 30mg	3. Amitriptyline 100mg, quetiapine 200mg	B (TRD 3)	6	1 (13 days)
6	M	70	F33.2	2 months		1. Escitalopram 20mg, pregabalin 150mg	A	6	3 (2 weeks)
7	F	68	Recurrent brief depression	7 years		1. Escitalopram 15mg	Not applicable	Not applicable	Not applicable

*Staging of treatment resistance according to the stages defined by Souery et al. (1999)

Approximately half a year later, the patient wished to become pregnant, and thus a reduction of psychopharmacologic treatment was once again initiated. Sertraline was tapered over 6 weeks and resulted in few problems. A month later, the patient began to taper AMS with the use of a liquid formulation. The reduction of the original 50 mg dose was extended over a 6-week period and was completed with smaller increments of reduction toward the end. When the patient had reached a dose of 5 mg, she started to feel uneasy. A few days after completely discontinuing AMS treatment, she became fearful and experienced panic attacks, anhedonia, a lack of drive, intolerance to stress, nausea, hot flashes, palpitations, and difficulty concentrating. Given the deterioration of symptoms, AMS was once again added to her treatment regimen at a dose of 50 mg. Although the patient felt much better after 4 weeks, the improvement was not as pronounced as before. Thus, AMS was increased to 100 mg, which led to complete improvement in her wellbeing. Two months later AMS was tapered again, which led to the same complaints as before.

Patient 5 (female)

This patient's depression had started 9 months prior to her inpatient treatment, around the time that she had suffered a lumbar discus prolapse accompanied by pain, paresthesia, and a slight palsy in the right leg. Her mood was low, with reduced drive. She deplored her pains and was pessimistic about her future and her sleep was severely disturbed. Now, her psychopharmacologic treatment was changed to amitriptyline and quetiapine. She then underwent vertebral surgery, which relieved the pain, but her depressive state remained unchanged. Nine weeks of inpatient treatment resulted in only moderate improvement in her depression. Augmentation with 50 mg AMS led to a dramatic change in her mood within a week. The patient gained energy and hope and could be discharged 13 days later.

AMS was tapered 6 months later, while amitriptyline and quetiapine remained unchanged. Over a 3-week period, AMS was reduced to a dose of 25 mg. When AMS was tapered to a dose of 12.5 mg, she complained about a transitory lowering of her mood. Three days after AMS was completely discontinued, symptoms became severe. The patient became severely depressed with ruminations and somatic complaints such as palpitations and an increase in lumbar pain. These symptoms did not improve after a week and thus AMS was started again at a dose of 25 mg, which quickly resolved her symptoms.

Patient 6 (male)

This patient was admitted to inpatient treatment for his third depressive episode. For approximately 3 years, he had been on a stable regimen of escitalopram, trazodone, and pregabalin. Eight weeks prior to his hospitalization, he underwent laparotomy for appendicitis, which led to the reemergence of a depressive state. His mood was low with a loss of drive and energy. He complained of anhedonia, rumination, agitation, loss of appetite, and disturbed sleep. To begin treatment, his dosage of escitalopram and pregabalin was increased. When no improvement had occurred after 3 weeks, 50 mg AMS was added to his regimen. With the addition of AMS, his mood improved considerably, and the patient was discharged in fair condition 2 weeks later. There were further improvements in his mood once at home, and he chose to discontinue AMS on his own, as he was unhappy about the number of pharmacologic agents that he had to use. He first reduced the dose to 25 mg and then completely discontinued after a week. Already at half dose, he felt tired and "overworked," with a slightly depressed mood. His state worsened considerably once he completely discontinued use of AMS. He reported feeling severely fatigued, yet also experienced unrest and stated: "When I lay down I feel uneasy and also when I stand up." He suffered from anhedonia, sleep disturbances, tremors, despair, and suicidal ideation, which motivated him to seek help at our outpatient clinic. When he resumed treatment with 50 mg AMS, his symptoms improved within a few days.

Patient 7 (female)

This patient has suffered from recurrent depressive episodes ever since giving birth to her daughter 30 years earlier. For approximately 7 years, she had been experiencing a rather constant pattern of severe, short depressive states that lasted for about 7 days and were followed by 3 weeks of a stable mood. These depressive fits were independent of external stimuli. She often perspired excessively the night before and would awake with a feeling that the depression had started. During these periods, she complained of a lack of energy and interest, a loss of appetite, and anhedonia, with some improvement of these symptoms toward the evening. On rare occasions, these depressive states extended over several weeks, but the predominant pattern was that of recurrent bouts of brief depression.

The patient has been receiving a 15 mg dose of escitalopram for more than 3 years. A trial of lithium was not effective. During one of these short, depressive periods, 50 mg AMS was added to her treatment regimen. Over the next 2 months, the depressive periods were shortened to 2 to 3 days. When the dose of AMS was increased to 100 mg, these depressive periods stopped almost completely, as the patient experienced only 1–2 "bad days" over a 6-month period. Within the first months of treatment, the patient gained 5 kg. She could avert further weight gain with a strict diet and exercise regimen yet reported an increased craving for sweet foods. The patient also reported some tenderness in her breasts. PRL levels were assessed and they were found to be elevated to 138 ng/ml. No abnormalities were detected with mammography. The patient has now been receiving

this treatment for approximately 3 years. Her dose of AMS was slowly reduced to 25 mg. Throughout the last year, she reported only 2 days of feeling depressed and to a lower extent than that previously experienced.

DISCUSSION

Effectiveness

As these cases show, AMS often works remarkably well for the treatment of depression, even in cases with a high grade of therapy resistance (patients 1, 3, and 5). Furthermore, a case of recurrent brief depression, which is typically considered difficult to treat (Baldwin et al. 2014), was substantially ameliorated by the addition of AMS to the treatment regimen (patient 7). Certainly, there are also patients who do not respond to AMS (not covered in this report) or whose response to AMS is doubtful (patient 4).

The antidepressive effects of low dosages of AMS have been firmly established for the indication of dysthymia (Komossa et al. 2010). The mode of action of AMS in depressive states remains unclear. Most authors attribute its antidepressive effect to the blockade of presynaptic D2 receptors, which increases dopamine turnover, or to a special affinity for mesolimbic and frontal neurons and a lack of inhibition of D1 receptors (Pani & Gessa 2002). Moreover it has been shown that AMS is a powerful antagonist of 5-HT7 receptors (Abbas et al. 2009, Mnie-Filali et al. 2011). In an animal model, AMS no longer mediated antidepressive effects in 5-HT7 knock-out animals (Abbas et al. 2009). Thus, the effect of AMS on 5-HT7 receptors may be more important than its effect on D2/3 receptors. In animal models, low dose coadministration of antidepressants and 5-HT7 antagonists resulted in effect potentiation, which lends support to the use of AMS as an augmentation agent (Leopoldo et al. 2011).

Tolerability

There are two side effects which dampen AMS' record of excellent tolerability. First, the increase in PRL, which sometimes may become symptomatic, with tenderness of the breasts, galactorrhea, amenorrhea, and loss of libido (patient 3,4,7). To our experience, PRL rises in all patients treated with AMS, usually to 100–200 ng/ml. In our practice, we follow the recommendation to tolerate elevated levels of PRL in asymptomatic patients and only react to patients who become symptomatic (Hummer & Huber 2004). In some instances, the effect of AMS had been very favorable and patients preferred to continue with treatment despite these side effects (patient 7). Though there is a report regarding successful treatment of risperidone-induced PRL elevation with dopamine agonists (Tollin 2000), we found no effect of cabergoline on patient 3. The elevation of PRL is a common side effect of drugs with a high affinity for

D2 receptors. AMS is a special case, however, as PRL levels do not correspond with AMS serum levels and, therefore, not with its occupation of D2/3 receptors in the central nervous system. This may be explained by poor blood-brain barrier penetration by AMS (Härtter et al. 2003). It has been postulated that AMS exerts its effect on PRL via the pituitary body, as it is situated outside of the blood-brain barrier (Bressan et al. 2004, Kapur et al. 2002).

Weight gain is the second side effect of AMS that is worth mentioning and that was not uncommon in our patients (patients 2 and 7).

Onset of action

A special feature of augmentation therapy with AMS is its early onset of action. The effects of AMS were already evident after a few days and were fully felt after 1 to 2 weeks in patients 1, 2, and 4–6; a response that is faster than is typical of antidepressant agents. Our experience with other augmentation agents, such as quetiapine, olanzapine, or aripiprazole, has led us to the conclusion that no other drug works as fast as AMS. An early onset of action has also been previously reported when AMS was used as a monotherapy (Amore et al. 2001, Hardoy & Carta 2010, Jori et al. 1998, Montgomery 2002, Racagni et al. 2004), as well as in some animal models of depression (Papp & Wieronska 2000).

Withdrawal

An unexpected finding was that it was often difficult to discontinue treatment with AMS (patients 3–6). Severe deterioration of mood was observed, even when tapering was very slow. The close relationship between dose reduction and deterioration of mood suggests that this is a withdrawal syndrome, rather than a recurrence of depression. The symptoms resembled the original depressive symptoms, yet with the unusual occurrence of intense anxiety, panic, and agitation, and disappeared when AMS treatment was reinstated. Theoretically, withdrawal symptoms should fade over time, whereas the recurrence of depression would be expected to persist. Our patients' symptoms were so dramatic that it was common for them to resume treatment on their own. Notably, the most severe withdrawal syndrome was in a patient in which the therapeutic effect of AMS was considered doubtful (patient 4). We were unable to find reports in the literature regarding withdrawal phenomena after AMS treatment, aside from anecdotal remarks by experts (Benkert & Hippius 2013, Montgomery 2002). The withdrawal syndrome that we observed in these patients closely resembled the "dopamine withdrawal syndrome," which has been described in patients who had discontinued use of direct dopamine agonists prescribed for Parkinson's syndrome (Pondal et al. 2013, Rabinak & Nirenberg 2010).

Table 2. Papers reporting on augmentation of antidepressants with AMS

Author	Population	Intervention	Results	Comments
Comparative trials				
Dyakonov & Lobanova 2014	Sixty-three patients with moderate to severe recurrent depressive episodes.	Treatment with 40 mg Fluoxetine + 10–15 mg Olanzapine vs. 100–150 mg Sertraline + 50–100 mg AMS for 40 days	Treatments were equally effective in both groups; both groups experienced a rapid onset in improvement.	Open label trial, allocation not specified
Rocca et al. 2002	Sixty outpatients with dysthymia who did not respond to a 3-month treatment period of 20 mg paroxetine.	Treatment with 40 mg Paroxetine vs. combination of 20 mg Paroxetine + 50 mg AMS for 3 months	Response/remission rate was 54%/32% with 40 mg Paroxetine and 56%/44% with the combination treatment (ns). Psychosocial functioning was better in the group receiving combination treatment (p=0.045).	Open label, randomized
Grigorescu et al. 2010a, b	Fifty-eight patients with MDD with atypical features.	TAU vs. AD + AMS for 8 weeks	AD + AMS sig. better on HDRS from week 1 forward. Endpoints: Response (TAU vs. AD + AMS): 55% vs. 42% (p<0.001); Remission: 34% vs. 25% (p<0.001)	Open study, group allocation not described.
Case reports				
Politis et al. 2008	Eleven elderly patients with psychotic depression. Prior treatment with either 20–40 mg citalopram or 30–60 mg mirtazapine for 4 to 6 weeks without improvement in psychotic symptoms.	Addition of 75–100 mg AMS	Six patients in full remission of depression, five patients in partial remission of depression. Resolution of psychotic symptoms in all patients.	Study focused on resolution of psychotic symptoms.
Carvalho et al. 2007	One patient, female, 35 years of age. Experienced a depressive episode and was prescribed citalopram, which was increased to 60 mg for 12 weeks without response.	Addition of 50 mg AMS	Remission within 2 weeks	
Hardoy & Carta 2010	Twenty female patients with MDD. No record of treatment resistance.	Treatment with 100 mg Fluvoxamine + 50 mg AMS for 6 weeks	Average HDRS Score decreased from 26.2 to 9.6 after 6 weeks. Nineteen of 20 patients showed clear improvement by day 14. No nausea at the onset of treatment (anti-nausea effect of AMS?)	No comparison group.
Pharmacoepidemiological study				
Ceskova 2011	Three thousand one hundred and seventy-eight patients with depression, reported by 257 outpatient psychiatrists.	Non-interventional study: Treating psychiatrists completed a questionnaire for every patient treated with an antidepressant + AMS	Effective for 87.7% of patients Of all patients, 43.1% observed a clinical effect in the second week of treatment Most common side effects: weight gain (26.4%), headache (18.9%), fatigue (18.5%), dry mouth (17.8%)	AMS 50 mg is licensed for dysthymia in the Czech Republic. It is common to prescribe a combination of AMS with other antidepressants. The purpose of the study was to assess the safety of combination treatment with AMS.

TAU: treatment as usual; AD: antidepressant; HDRS: Hamilton Depression Rating Scale; MDD: Major Depressive Disorder

Literature on augmentation with AMS

A search of the literature revealed only a small number of papers that addressed augmentation therapy with AMS (summarized in Table 2). There have been three open comparative studies with approximately 60 participants each, and only one in which the allocation to treatment groups was random (Rocca et al. 2002). In this study, dysthymic patients who did not respond to 20 mg of paroxetine over a 3-month period received either 30 mg paroxetine plus 50 mg AMS or 40 mg paroxetine for an additional 3 months. There was equal improvement on depression ratings in both groups, and the group receiving AMS as an augmentation therapy had significantly higher ratings on the Global Assessment of Functioning scale. Grigorescu et al. (2010a) compared standard antidepressant therapy with standard antidepressant therapy plus AMS in patients with depression with atypical features and determined that remission rates were significantly higher in the latter. D'yakonov and Lobanova (2014) showed that a combination of fluoxetine and olanzapine was as effective as a combination of sertraline and AMS in the treatment of patients with depression. In summary, these studies, which are of modest methodological quality, showed that augmentation with AMS is as effective as an increase in dosage of a selective serotonin reuptake inhibitor (SSRI) or as augmentation with olanzapine, and is superior to SSRI monotherapy.

There are also three case reports or case series that describe favorable outcomes of AMS augmentation therapy in patients with and without treatment resistant depression (Carvalho et al. 2007, Hardoy & Carta 2010, Politis et al. 2008). Finally, a study conducted in the Czech Republic examined the experiences of outpatient psychiatrists who had prescribed a combination of antidepressants and AMS. The safety of this combination, which was the focus of this study, was shown to be good. This and four other reports (Amore et al. 2001, Carvalho et al. 2007, Hardoy & Carta 2010, Jori et al. 1998) described a rapid onset of action (within 1 to 2 weeks) of AMS treatment, similar to that which was observed in our study.

Our observations of the effectiveness of AMS in otherwise treatment-resistant patients, its early onset of action, and the spectrum of related side effects are in line with previous findings. To our knowledge, there have been no reports on the effects of discontinuing AMS. This was somewhat unexpected, as we have experienced such effects in patients beyond these described here and consider them not very rare.

Limitations

Our study cannot provide definitive proof that augmentation therapy with AMS led to the improvement seen in our patients' depressive symptoms. It is possible that these improvements may have been due to an even-tual response to the previous treatment, to a placebo effect or to a spontaneous remission. Furthermore, no comprehensive rating instruments were employed in our descriptions of these cases. When data are gathered in an outpatient setting, reports rely on patients' accounts and not on direct observation.

In addition, our selection of cases may have conferred a bias in our assessments of effectiveness and the occurrence of withdrawal syndromes. Overall, raw estimation suggests that around 50% of patients do respond to AMS and only a minority of patients (5–10%) have withdrawal symptoms upon discontinuation of AMS treatment. For the purposes of this paper, cases were selected in which our findings were most interesting in these respects.

CONCLUSIONS

We consider AMS to be an effective augmentation agent for the treatment of depression. Special features of this drug include its level of effectiveness and its early onset of action. Side effects are negligible, aside from weight gain and an increase in PRL levels, which occur even at the low doses used to treat depression. Some of our patients presented with a withdrawal syndrome that resembled the withdrawal that is often observed upon removal of direct dopamine agonists.

In our view, augmentation with AMS to treat depression is an underused strategy and should be further explored by means of randomized controlled trials. Beyond this, the mode of action of AMS appears to differ not only from antidepressants, but also from other augmentation agents. Further clarifications of its mode of action may lead to new avenues for investigation into antidepressant treatment.

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Correspondence:

Univ. Prof. Dr. Hans Rittmannsberger, MD
Department of Psychiatry, General Hospital Steyr
4400 Steyr, Austria
E-mail: h.rittmannsberger@aon.at