Treatment of Depression With Methylphenidate in Patients Difficult to Wean From Mechanical Ventilation in the Intensive Care Unit

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Background: Mechanical ventilation is often required to support patients in the intensive care unit (ICU) with life-threatening cardiovascular, respiratory, or neuromuscular disorders. Occasionally, difficulties related to weaning patients from this support occur owing to depression. The traditional and newer-generation antidepressant drugs have a relatively long latency of response that interferes with rehabilitation attempts in the ICU. Psychostimulants such as methylphenidate show a rapid onset of antidepressant activity and a benign side effect profile.

Method: As consulting psychiatrists in the consultation-liaison service of a university hospital, we treated 7 patients with complex ICU courses presenting prolonged mechanical ventilation and psychomotor retardation associated with markedly depressed mood (DSM-IV criteria) by giving them methylphenidate. Methylphenidate was started on the first day at a dose of 2.5 mg p.o. in the morning and was increased by 2.5 mg each day with twice-a-day dosing in the morning and at noon until the patient responded or showed side effects. A maximum dose of 15 mg/day was not exceeded. Outcome evaluation was performed using the Clinical Global Impressions scale.

Results: Five (71%) of 7 patients showed marked or moderate improvement in mood and activity within 3 to 4 days, and discontinuation of ventilator support was achieved within 8 to 14 days. Side effects with these 5 patients were not encountered. Of the remaining 2 patients (29%), 1 developed psychomotor agitation and anxiety within 4 days. Another patient showed only minimal improvement with regard to activity.

Conclusion: Methylphenidate might be a rapidly effective and safe treatment for depression in difficult-to-wean patients hospitalized for life-threatening medical illness in the ICU. Implications for future research for this population of patients warrant formal randomized, prospective, clinical case-control evaluation.

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Mechanical ventilation is often required to support patients with life-threatening respiratory failure. Such failure may be caused by lung parenchymal disease (e.g., adult respiratory distress syndrome [ARDS], pneumonia), neuromuscular disorders (e.g., myasthenia gravis, Guillain-Barré syndrome), cardiovascular failure (e.g., acute myocardial infarction), and/or sepsis. The length of time that patients are mechanically ventilated depends on their clinical condition. Eighty percent of the intensive care unit (ICU) patients return to spontaneous breathing in less than 12 hours; the remaining 20% require a gradual and progressive withdrawal from the ventilatory support over a period of several days or weeks.[1] Rarely, the weaning process may prove to be impossible, and one major problem associated with prolonged mechanical ventilation is a high risk for the development of nosocomial infections.[2] Estimates of the high cost and negative outcomes in the context of prolonged ventilation vary.[3]

Medical causes of weaning failure are numerous, including respiratory drive insufficiency, respiratory muscle weakness, and increased respiratory workload. The usual reason, however, that patients cannot be weaned from ventilators is a combination of pulmonary disease and interaction with the anxiety of dyspnea. Thus, both physical and psychological factors may hinder weaning and therefore should be considered when treating difficult-to-wean patients.[4] Various therapies have been used to facilitate weaning, including ventilatory muscle training,[5] pharmacologic therapy with analgesics and sedatives,[6] biofeedback, and relaxation.[7,8] Symptoms such as anxiety, discomfort, anger,

fatigue, and depression are viewed as negative and counterproductive to the weaning process.[9] In this context, an interdisciplinary approach addresses the patient's anxiety, sleep deprivation, lack of appetite, decreased communication, decreased activity, dyspnea, knowledge deficit about dyspnea and weaning, lack of self-confidence, and decreased verbalization by implementing biofeedback, positive reinforcement, teaching about dyspnea and weaning, and involvement of the patient's family in providing some of these interventions.[10] Occasionally, psychological factors such as anxiety and depression are considered as the main reasons for failure of weaning attempts.[11]

From a psychiatric point of view, clinical observations and experience point to 2 subgroups of difficult-to-wean patients: on the one hand, patients develop ventilator dependence owing to severe anxiety and panic associated with dyspnea when they discontinue mechanical support during weaning. Adequate treatment approaches involve medications such as benzodiazepines and/or biofeedback to control anxiety. However, anxiolytics can result in sedation and lethargy, and biofeedback is time consuming and requires specialized skills by a multidisciplinary team. On the other hand, some patients are not trying to breathe during the weaning process because they are apathetic and depressed secondary to depression.[12] Depressive symptomatology, indeed, is frequently found secondary to underlying chronic or severe medical illnesses.[13] Hence, antidepressants may facilitate weaning. Nevertheless, the traditional (e.g., tricyclic antidepressants [TCAs]) and newer-generation (e.g., selective serotonin reuptake inhibitors [SSRIs]) antidepressant drugs usually take between 2 and 3 weeks to exert a therapeutic effect. In contrast, psychostimulants such as methylphenidate show a rapid onset of antidepressant activity and a benign side effect profile in patients with secondary depression in medical illness.[14,15] They therefore might be especially useful in difficult-to-wean ICU patients who cannot afford to wait a couple of weeks until depressive symptoms improve.

To our knowledge, only 1 case report[16] has been published to date that described the possible utility of methylphenidate in a depressed "hard-to-wean" patient. We report on 7 methylphenidate-treated patients who were experiencing complex ICU courses and undergoing prolonged mechanical ventilation associated with depression and psychomotor retardation.

METHOD

Patient Population

Seven patients treated for life-threatening respiratory failure at various specialized ICUs of the tertiary care hospital of the Ludwig-Maximilians University of Munich, Germany, were referred to the psychiatric consultation service in 1998 and 1999 to assess presumed depression related to the complicated weaning process. The causes of respiratory failure were myasthenia gravis (N = 1), ARDS (N = 1), pneumonia (N = 1), acute myocardial infarction (N = 1), exacerbation of chronic obstructive pulmonary disease (COPD) (N = 1), and respiratory muscle weakness due to critical illness polyneuropathy after cardiac surgery (N = 2).

By the day of psychiatric evaluation, the duration of mechanical ventilation ranged from 19 to 48 days (median = 30 days), and several attempts of weaning trials had been unsuccessful. The weaning mode implied T-piece trials alternating with assist/control mode ventilation. The weaning process was performed when a phase of clinical stability was reached: the underlying reason for mechanical ventilation was resolved, severe medical factors (e.g., acid-base abnormalities, infection, shock, renal failure) were corrected, and important weaning readiness parameters (e.g., awake and alert, positive end-expiratory pressure ≤ 5 cm H_2O, arterial partial pressure of oxygen [P_{AO_2}] > 60 mm Hg on a fraction of inspired oxygen [F_{IO_2}] < 0.50, arterial partial pressure of carbon dioxide [P_{ACO_2}] acceptable with pH of 7.35 to 7.45) were met.

In a brief psychiatric interview in the ICU, experienced psychiatrists from the consultation service (H.-B.R., S.E., H.-P.K.) assessed the patients. They found the patients to have psychomotor retardation and marked depression as determined by evaluating the core symptoms of depressive illness (sadness, anhedonia, feelings of worthlessness, pessimistic thoughts, loss of energy—DSM-IV criteria). Patients with acute suicidality, psychotic features including Schneider's first rank symptoms, delirium, alcohol-related disorders, psychoactive substance abuse, and use of monoamine oxidase inhibitors (MAOIs) within 8 weeks were excluded from the study. One patient had a psychiatric history of seasonal depression. Three of the 7 patients were receiving antidepressant medication: 2 patients were administered the third-generation antidepressant paroxetine, an SSRI that is considered a safe drug in patients with somatic diseases with 24-hour half-life and with no active metabolite,[17] and 1 patient was given the second-generation antidepressant viloxazine, a newer TCA with a unique structure and a relatively short half-life (1 to 2 hours) and a favorable side effect profile regarding anomalies in electrical conduction and after myocardial infarction.[17,18]

All patients were deemed able to give informed consent. The main patient characteristics are depicted in Table 1.

Regimen

Methylphenidate was started on the first day at a dose of 2.5 mg p.o. at 7:30 a.m. The dose was increased by 2.5 mg each day with twice-a-day dosing at 7:30 a.m. and noon until the patient responded or had side effects. The prospectively defined maximum dose of 15 mg/day was not exceeded. To avoid insomnia, dosing of methylpheni-

Table 1. Patient Characteristics and Treatment Data on Day of Psychiatric Assessment and Before Methylphenidate Administration (N = 7)[a]

Patient	Age (y)	Gender	Somatic Reason for Mechanical Ventilation	Duration of Mechanical Ventilation (d)	Antidepressant Drug Treatment (mg/d)	Previous Psychiatric History	Referring ICU Speciality
1	65	Male	Pneumonia	26	...	...	Cardiology
2	75	Female	Critical illness polyneuropathy after cardiac surgery	39	...	...	Heart surgery
3	78	Female	Critical illness polyneuropathy after cardiac surgery	19	...	...	Heart surgery
4	55	Male	ARDS	48	20 mg paroxetine po	...	General surgery
5	73	Male	Acute myocardial infarction	30	300 mg viloxazine iv	...	Cardiology
6	84	Female	Exacerbation of COPD	23	...	...	Cardiology
7	38	Male	Myasthenia gravis	32	40 mg paroxetine po	Seasonal depression	Neurology

[a]Abbreviations: ARDS = adult respiratory distress syndrome, COPD = chronic obstructive pulmonary disease, ICU = intensive care unit.

date after 4 p.m. was not recommended. After improvement or remission of symptoms of depression and psychomotor retardation, methylphenidate was tapered over a period of 1 to 2 weeks. If side effects occurred, the dose was immediately decreased by 2.5 mg per time of administration (5 mg each day) and finally discontinued.

Outcome Evaluation

Clinical response was prospectively assessed using the efficacy categories of the Clinical Global Impressions scale (CGI),[19] which was applied every day in the late afternoon after any changes in dosage were made. The efficacy index of the CGI comprises two 4-point scales: one 4-point scale assesses the therapeutic response (1 for "marked improvement," 2 for "moderate improvement," 3 for "minimal improvement," and 4 for "unchanged or worse"), and the other evaluates the degree of side effects (1 for "none," 2 for "do not significantly interfere with patient's functioning," 3 for "significantly interfere with patient's functioning," and 4 for "outweigh therapeutic effect"). The course of weaning was clinically rated by the referring physicians in the ICU during unit rounds.

RESULTS

The mean age of the 7 assessed patients was 66.9 years (range, 38–84 years); 3 were women, and 4 were men. Psychiatric diagnoses included depressive disorder not otherwise specified (N = 6) and major depressive disorder with seasonal pattern (N = 1) according to DSM-IV.

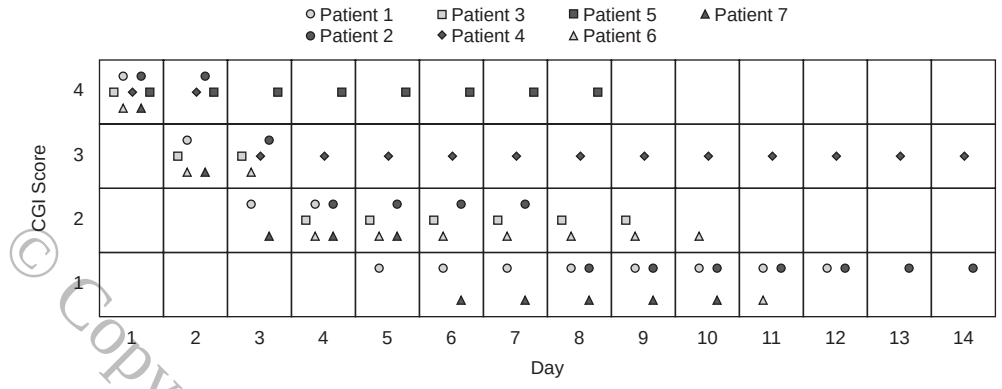
CGI ratings of psychostimulant response to methylphenidate are summarized in Figure 1. Five (71%) of 7 patients (patients 1, 2, 3, 6, and 7) had either a moderate or marked response to methylphenidate. Depressive symptoms including psychomotor retardation improved within 3 to 4 days. The weaning process was completed within 8 to 14 days, and the patients were transferred to the medical wards or to rehabilitation centers specialized for patients after prolonged intensive care outside the university hospital. No side effects were observed. Patient 4 showed only minimal improvement with regard to activity. Methylphenidate, 10 mg/day, was discontinued after 2 weeks, while paroxetine was maintained at 20 mg/day. Adverse side effects, including cardiac arrhythmias, were not encountered. In patient 5, the dose of viloxazine was reduced from 300 mg/day to 100 mg/day i.v., while methylphenidate was augmented to 10 mg/day p.o. within 4 days. Patient 5 developed psychomotor agitation and anxiety within 4 days after beginning methylphenidate. The adverse effects could be related to the psychostimulant coadministration. The daily methylphenidate dose of 10 mg therefore was tapered over 4 days, and adverse effects abated. Viloxazine was again increased to 300 mg/day, and patient 5 was transferred to the medical ward 11 days after methylphenidate discontinuation.

Patients were treated for a mean ± SD of 11 ± 3 days. The mean daily dose of methylphenidate was 6.37 mg (range, 5–15 mg).

DISCUSSION

Little is known concerning definitive treatment of depressive symptoms in severely ill ICU patients who do not successfully respond to conventional weaning from mechanical ventilation. Many factors can prolong the weaning process, including insufficient nutrition, generalized muscular fatigue, problems with secretion management, and psychological considerations. Only a few studies have included psychological factors as independent variables affecting patients' readiness to wean: anxiety,[20] fatigue and depression,[21] and patient's perception of dyspnea during weaning[22] were linked to weaning success.

Figure 1. Therapeutic Response According to the Efficacy Index of the Clinical Global Impressions Scale (CGI)



In a case report, Johnson et al.[16] described the possible utility of methylphenidate in 2 depressed hard-to-wean patients in the ICU. One patient was treated with a maximum dose of 10 mg in the morning. Four days after starting methylphenidate treatment, the patient was extubated and was discharged from the ICU to a medical ward. Overall, he received methylphenidate for a duration of 8 days without developing side effects. The other patient was administered 5 mg of methylphenidate in the morning for 2 days. She experienced adverse effects such as anxiety, restlessness, and nocturnal insomnia that resolved within 24 hours after discontinuing methylphenidate.

Our experience with methylphenidate in depressed difficult-to-wean ICU patients hospitalized for life-threatening somatic disorders was striking and encouraging. In 5 of 7 patients, we found impressive improvements in mood, activity, and respiratory efforts after beginning methylphenidate, which had a relatively rapid onset of action without treatment-related adverse side effects (see Figure 1). Methylphenidate is chemically an amphetamine that is derived from β-phenylethylamine; methylphenidate is thus also known by its chemical name of methyl α-phenyl-2-piperidineacetate hydrochloride. It is a weak base; the absorption after oral administration is rapid and complete, achieving peak blood levels within 1.5 to 2.5 hours without producing active metabolites. It has a short elimination half-life of 2 to 3 hours.[23] The precise mechanism of action of methylphenidate is still not clear; however, it is known that methylphenidate causes various biological effects leading to enhanced central and peripheral noradrenergic activity. Evidence suggests that methylphenidate exerts its effects by displacing dopamine from *prepackaged* storage vesicles into the synaptic cleft, leading to enhanced biological activity of the biogenic amines. Pretreatment with reserpine prevents dopamine displacement by methylphenidate.[23–25] Recently, it has been reported that methylphenidate and cocaine have similar affinities for the dopamine transporter, specifically in the striatum, but methylphenidate has a longer clearance than cocaine.[26] Its clinical use encompasses the treatment of attention-deficit/hyperactivity disorder and narcolepsy. It also has been used experimentally as an antidepressant in the treatment of medically ill elderly patients, cancer patients, poststroke patients, human immunodeficiency virus (HIV)-positive patients, patients with head injury and epilepsy, and patients with pain.[27] There is no basis for methylphenidate abuse in these medical indications.[28]

Five of our 7 patients had diagnosable depressive disorders that did not meet the criteria for major depressive disorder, dysthymia, adjustment disorder with depressed mood, or organic mood disorder as defined by DSM-IV.[29] They therefore were diagnosed "not otherwise specified," but association with severe medical condition was presumed. Patient 7, who had a history of seasonal depression, met DSM-IV criteria for major depressive disorder. He was already taking an antidepressant (paroxetine, 40 mg/day), and low-dose methylphenidate (up to a maximum of 5 mg in the morning) used as an adjunct could be effectively and safely added.

Our finding supports previously noted reports of a rapid, safe, and efficacious methylphenidate augmentation of SSRIs in patients with major depression.[30] However, 1 of the 2 patients (patient 4) who did not respond to methylphenidate received simultaneous paroxetine (20 mg/day) and methylphenidate (up to a maximum of 10 mg/day). A possible explanation is that an adequate therapeutic dose was not reached. The other patient (patient 5) was on viloxazine treatment and did not tolerate the addition of methylphenidate to viloxazine even though the dosage of the newer TCA was considerably decreased from 300 mg/day to 100 mg/day. An unfavorable drug interaction was probably responsible for the adverse side effects (psychomotor agitation and anxiety). It has been reported that TCAs (e.g., imipramine) are potentiated by amphetamine (interference with hepatic aromatic hydroxylation of TCAs); on the

other hand, TCAs potentiate amphetamine by increasing brain concentrations of amphetamine.[31]

Four of our 7 patients received methylphenidate monotherapy and responded to it moderately or markedly. The effectiveness of methylphenidate in this population might be associated with its action in the central nervous system, producing wakefulness, alertness, elevation of mood and self-esteem, and increased motivation, thus implying improved physical performance and respiratory effects. Methylphenidate can produce a range of cardiovascular (e.g., arrhythmias, tachycardia, palpitations), gastrointestinal (e.g., anorexia, vomiting, cramping), and central nervous system (e.g., agitation, restlessness, confusion, psychosis, insomnia) side effects,[27] but they were not encountered in this subgroup of patients. This finding may be due to the low doses and short time of methylphenidate treatment in our clinical observations. In this context, it is worth mentioning that the manufacturers of methylphenidate recommend a dosage range from 2.5 to 60 mg/day when methylphenidate is used for the approved indications of attention-deficit/hyperactivity disorder and narcolepsy. The lack of adverse effects associated with methylphenidate use in our patients may also be related to our careful psychiatric assessment that excluded difficult-to-wean patients with predominant anxious and psychomotor-agitated features from methylphenidate treatment. They were administered benzodiazepines such as clorazepate or lorazepam.

To deepen discussion, we want to emphasize that the clinical challenge for the consultation-liaison psychiatrist was to ascertain whether the weaning process was complicated owing to the patients' severe anxiety of dyspnea or owing to their depressed mood and apathetic state secondary to depression. Administration of methylphenidate to enhance the weaning process would probably be counterproductive to anxious and agitated patients, since methylphenidate can worsen agitation, restlessness, and insomnia. Methylphenidate can eventually produce cardiovascular disturbances such as palpitations, sweating, and tachycardia. These side effects commonly increase anxiety or even mimic panic attacks. We thus excluded this subgroup of difficult-to-wean patients in the ICU from methylphenidate treatment. They would rather benefit from anxiolytics and, if available, biofeedback or relaxation techniques. Basically, it should be the responsibility of the consultation-liaison psychiatrist—based on thorough history taking and assessment of the present mental state—to evaluate the psychological factors in the weaning patients and to recommend appropriate interventions to manage their psychological problems.

CONCLUSION

Methylphenidate monotherapy is a rapidly effective and safe treatment for depression in patients hospitalized for life-threatening illness in the ICU who are difficult to wean from mechanical ventilation. Despite the shortcomings of these clinical observations that did not employ blinding or control groups, we would encourage further research for this population of patients with prospective study designs and random allocation, since it is of paramount importance to establish a rapidly effective and safe treatment for them.

Drug names: clorazepate (Tranxene), lorazepam (Ativan and others), methylphenidate (Ritalin and others), paroxetine (Paxil), reserpine (Serpasil and others).

REFERENCES

1. Shapiro B, Kacmarek RM, Cane RD, et al. Clinical Application of Respiratory Care. 4th ed. Chicago, Ill: Yearbook Medical; 1991
2. Lemaire F. Difficult weaning. Intensive Care Med 1993;19:69–73
3. Cohen IL, Lambrinos J, Fein IA. Mechanical ventilation for the elderly patient in intensive care: incremental changes and benefits. JAMA 1993; 269:1025–1029
4. Weilitz PB. Weaning a patient from mechanical ventilation. Crit Care Nurs 1993;13:33–41
5. Aldrich TK, Karpel JP, Uhrlass RM, et al. Weaning from mechanical ventilation: adjunctive use of inspiratory muscle resistive training. Crit Care Med 1989;17:143–147
6. Carroll KC, Magruder CC. The role of analgesics and sedatives in the management of pain and agitation during weaning from mechanical ventilation. Crit Care Nurs Q 1993;15:68–77
7. Acosta F. Biofeedback and progressive relaxation in weaning the anxious patient from the ventilator: a brief report. Heart Lung 1988;17:299–301
8. Holliday J, Hyers T. The reduction of weaning time from mechanical ventilation using tidal volume and relaxation biofeedback. Am Rev Respir Dis 1990;141:1214–1220
9. Burns SM, Clochesy JM, Hanneman SK, et al. Weaning from long-term mechanical ventilation. Am J Crit Care 1995;4:4–22
10. Jacavone J, Young J. Use of pulmonary rehabilitation strategies to wean a difficult-to-wean patient: case study. Crit Care Nurs 1998;18:29–37
11. Tobin MJ, Yang K. Weaning from mechanical ventilation. Crit Care Clin 1990;6:725–747
12. Rothenhäusler HB, Kapfhammer HP. Psychiatric emergencies: consultation-liaison service in general hospitals. Psycho 1999;25:550–565
13. Rodin G, Voshart K. Depression in the medically ill: an overview. Am J Psychiatry 1986;143:696–705
14. Satel SL, Nelson JC. Stimulants in the treatment of depression: a critical overview. J Clin Psychiatry 1989;50:241–249
15. Masand P, Pickett P, Murray GB. Psychostimulants for secondary depression in medical illness. Psychosomatics 1991;32:203–208
16. Johnson CJ, Auger WR, Fedullo PF, et al. Methylphenidate in the "hard to wean" patient. J Psychosom Res 1995;39:63–68
17. Goodnick PJ. Pharmacokinetic optimisation of therapy with newer antidepressants. Clin Pharmacokinet 1994;27:307–330
18. Tikal K, Hrabankova M. Indications for antidepressive agents in relation to diseases of the cardiovascular system. Cesk Psychiatr 1993;89:163–165
19. Van Riezen H, Segal M. Comparative Evaluation of Rating Scales for Clinical Psychopharmacology. New York, NY: Elsevier; 1988
20. Jenny J, Logan L. Promoting ventilator independence: a grounded theory perspective. Dimensions Crit Care Nurs 1994;13:29–37
21. Higgins PA. Patient perception of fatigue while undergoing long-term mechanical ventilation: incidence and associated factors. Heart Lung 1998;27:177–183
22. Bouley GH, Froman R, Shah H. The experience of dyspnea during weaning. Heart Lung 1992;21:471–476
23. Waslick B, Greenhill LL. Psychostimulants. In: Lieberman JA, Tasman A, eds. Psychiatric Drugs. Philadelphia, Pa: WB Saunders Co; 2000:168–192
24. Huey LY, Janowsky DS, Judd LL, et al. Effects of lithium carbonate on MPH-induced mood, behavior, and cognitive processes. Psychopharmacology (Berl) 1981;73:161–164
25. Seiden LS, Sabol KE, Ricaurte GA. Amphetamine: effects on catecholamine systems and behavior. Annu Rev Pharmacol Toxicol 1993;33:

639–677
26. Volkow ND, Ding Y-S, Fowler JS, et al. Is methylphenidate like cocaine? studies on their pharmacokinetics and distribution in the human brain. Arch Gen Psychiatry 1995;52:456–463
27. Masand PS, Tesar GE. Use of stimulants in the medically ill. Psychiatr Clin North Am 1996;19:515–547
28. Klein RG, Wender P. The role of methylphenidate in psychiatry. Arch Gen Psychiatry 1995;52:429–433
29. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
30. Stoll AL, Pillay SS, Diamond L, et al. Methylphenidate augmentation of serotonin selective reuptake inhibitors: a case series. J Clin Psychiatry 1996;57:72–76
31. Garattini S, Jori A, Samanin R. Interactions of various drugs with amphetamine. Ann N Y Acad Sci 1976;281:409–425