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Pharmacological means to improve patients' mood. Are they effective and safe?

Abstract

Low mood and depression can be treated with many non-pharmacological means. However, in terminally ill these means are sometimes insufficient and the doctors need to prescribe drugs. In this article I shall discuss simple and proven drugs that improve patients mood and, some of them do have proven anti-depressant activity. I shall discuss methylphenidate, ketamine, cannabinoids and buprenorphine in more detail. Cautious use of these drugs in different clinical situations may improve nearly instantly quality of life and quality of dying. However, unskilled use of some of them may result in earlier death, neurosis, epilepsy and even psychosis.

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Key words: mood enhancement, low mood, depression antidepressant activity, methylphenidate, ketamine, cannabinoids, buprenorphine

Introduction

Terminally ill patients have many reasons to have their mood reduced or even being depressed. In fact, depression is not uncommon in terminally ill and is frequently and specifically associated with desire to hasten death [1–4]. The reason for this can be looked at their poor existential prospects, but also increasing anxiety, pain and other symptoms, changing relationships with others, changing roles, but also everyday chores and problems which usually are met as a challenge, in terminally ill they may be seen as impregnable bastions.

Low mood (dysthymia) is a part of depression. However, low mood can occur without depression, is more volatile and has a tendency to change for better while depression is more established low mood, with a tendency to get better. Low mood can be associated with low self-esteem, worrying, tiredness, frustration and sadness. With time it may progress to major depression and some other characteristics are being added to like hopelessness and helplessness, energy loss, pessimistic outlook, disturbed sleep pattern, social withdrawal and isolation, changes in appetite, suicidal or self-destructive thoughts.

Primarily, the decreased mood should be treated with good pain and symptom control, attention to psychological, social and spiritual problems but not tackled pharmacologically. When these measures are inadequate and/or ineffective the doctor may consider pharmacological "boosting" of the mood.

This article will concentrate on the situations where the patients' mood is depressed but there are no other

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means available to increase it other than drugs. This mood increase should happen rapidly and is needed only for a short time. We shall not discuss the cognitive behavioural therapy as it was discussed in detail elsewhere [5, 6]

It happens sometimes that undepressed patient takes an antidepressant for pain or other ailment (like pruritus) and after couple of hours or days discovers that he/she feels better, that his/her life is much more enjoyable. Does it mean that this person suffered of undiagnosed depression? Probably not. He experienced mood improvement, which may precede or even be independent of antidepressant effect. Mood improvement is usually rapid and short lived. After taking of some drugs it can appear within hours, but it may wear off in a couple of days leading to tolerance or even dependence (for example in case of methylphenidate (MPH) [7]. For a difference, antidepressant effect of drugs takes many days or weeks to occur, tolerance and dependence are rarely seen. Most antidepressant will with time improve the mood, but it may take many days or weeks before this will be obvious.

Is mood enhancing always a good thing to do in terminally ill? Probably not, and it need quite a debate with patient and his/her family. For example, cocaine and amphetamines, in short term, through activation of the sympathetic nervous system are able to boost patients' mood, energy and motivation. However, after an upward shift the patient may experience a downward one. In a critically ill patient it happened to me that "boosting up" his mood with methylphenidate (MPH) had an opposite effect: the patient did not appear more aroused but appeared to be anxious and died sooner that expected, living us in doubt. This effect could be compared to kicking-up a horse that is lying down (healthy horses always stand, never lie down). Kicking it up hard may speed his death.

Another problem is that mood enhancers may sometimes be inappropriate and mood improvement, especially in the presence of depression, can be experienced by a patient an unsuitable, confusing or wrong behaviour. A patient with a metastasised breast cancer, a retired paediatrician, reported that she came back home after a bad-news-session in hospital in a very low mood. Her friend doctor gave her a tablet with mianserin after which her mood improved rapidly. She became very talkative, laughed frequently and made a good impression on the relieved family. However, afterwards she told that she felt horrible being so joyful in such a situation discussing with her family serious matters.

Finally mood enhancement may be, especially by older patients, associated with a wrong behaviour burdened by the danger of abuse and addiction. Many of these drugs that we propose have "high street value" and because of this are declined by our patients. Some mood enhancers, actually, taken often and in inappropriate doses may appear to be addictive or at least their effect may diminish in time perpetuating feeling of hopelessness and defeat.

However, mood enhancing is certainly an option in patients with a limited prognosis who will die before experiencing an antidepressant effect of a tricyclic antidepressant.

In this article I shall review a couple of drugs that may be used as mood enhancers in palliative care. The list of these drugs is long and it is increasing daily. I shall concentrate here on those few with confirmed efficacy and with which I personally have an experience (good or bad, does not matter). I shall not discuss typical antidepressants, which produce mood improvement as this literature is well known and does not need replication.

Methylphenidate

Methylphenidate (MPH, Ritalin®) is a piperidine derivative structurally related to amphetamine. Pharmacological effects are also similar to amphetamine. It belongs to mild CNS stimulants with more prominent effects on mental than on motor activities. It has been used to treat opioid induced hypopnea, opioid induced sedation, attention deficits syndromes, cancer induced fatigue, recovery of the day and night rhythm (often adverse effects of opioids too) and more recently as mood enhancers and rapidly acting antidepressant [8]. MPH shares with Amphetamine also potential of abuse and generalised convulsions. I personally treated one patient with bronchial carcinoma and opioid-induced sedation with MPH and this patient developed serious epileptic attack. After brain MRI we discovered multiple brain metastases. So it is possible that MPH may lower the threshold for convulsions in case of unknown brain pathology.

However, the most interesting is the mood enhancing and antidepressive property of MPH. The antidepressant effect of MPH has been noticed in early nineteen-sixties [9]. Since that time MPH had been used occasionally when the patients did not tolerate tricylics [10, 11]

In an open clinical trial 34 patients with major depressive disorders were challenged with dexamethasone suppression test and subsequently with MPH challenge. It appeared that patients who experienced suppressed cortisol levels after dexamethasone did not respond to MPH, but responded well to amitriptyline. The other group without cortisol depression after dexamethasone responded well to MPH and to

imipramine [12]. This suggested for the first time that major depressive disorders is a highly heterogeneous group and MPH works on depression in a different way than some tryicyclics do and may be used to treat depression in resistant cases. Patients experienced mood-enhancing effect 1–3 days after commencing therapy. The heterogeneity of depression disorders and different responses to different antidepressants including MPH has been confirmed by other groups [13].

However, many of controlled clinical trials when MPH was compared to placebo did not confirm antidepressant effect [14, 15] this despite short-term positive effects on mood. It appears that MPH is able to enhance effects of other antidepressant drugs like citalopram [16] but this may result in enhanced toxicity of the combination and even danger of the serotonin syndrome [17]. As it will be explained later, lack of effect in comparison to placebo does not necessarily means that MPH is a useless drug.

So, in conclusion. MPH is an interesting CNS stimulant that shows a mood improving capacity, which may be independent or different from the antidepressant effect. MPH is able to enhance working of other antidepressant drugs. The mood enhancing effect appears rapid, within days, but may be short lived. Despite negative effects of many trials MPH is worth to try in resistant cases of depression.

Ketamine

Ketamine (KET) is a congener of phenylciclidine and is for many decennia known as a cheap dissociative anaesthetic. It is especially valued in the medically ill patients as it does not decrease blood pressure, does not induce bronchospasm and is generally safe with children. It is provided as a racemic mixture even though the S-isomer is known to be more potent and less toxic. A preparation containing only S-isomer is many times more expensive making it unavailable for poor countries. KET is believed to act on the NMDA receptor.

KET is preferentially administered IV and there is a controversy about the activity of KET after oral administration. KET has been used in subanaesthetic doses for the treatment of chronic pain [18]. KET was thought to enhance effects of opioids. Recent systematic reviews fail equivocally to confirm effects of KET in chronic pain [19, 20]. However, KET remains an important rescue 3rd line drug when anything else failed [18].

The mood improving ability and antidepressant effects of KET were noticed only recently [21]. This effect appeared long-lasting and within hours after a single IV dose of KET. This has been later confirmed by others [22, 23] Berman et al. suggested for the first time that the antidepressant effect of KET is using a glutaminergic pathway and suggested that this is why KET is effective in therapy resistant cases. Since this time KET as antidepressant developed further and a number of systematic analyses were performed and confirmed the observed effects [24–28]. KET as antidepressive drug is a hot topic now and some psychiatrist submit that KET is one of the most effective antidepressants ever discovered. To summarize data from numerous trials and analyses one can say that: KET works rapidly, mostly within 24 hours (mood improvement). 25% of patients experience remission of their depression within a week, but in some trials the remission rates are much higher. More than half of the trials (60%) were done with IV KET in single or repeated doses. IV Administration seems to be more effective than oral, and multiple doses (usually of 0.5 mg/kg per infusion) are more effective than single doses.

Other NMDA receptor antagonists have been studied too and it appears that they have less clear mood improving and antidepressant effect in comparison with KET but with decreased number of adverse effects. However, development of novel glutaminergic antidepressants is still possible and highly desirable.

From the point of view of palliative care it is important that Ketamine should be probably drug of choice in depressed patients considering suicide. In this way the need of IV administration is not a barrier, but an advantage.

Cannabinoids

Cannabinoids' ability to make people happy is legendary and its use has been practised for recreational purposes for centuries. It may be the most often used illicit drug in the world. There is some belief that cannabinoids use may benefit patients in chronic pain or spasticity that does not respond to conventional treatments. However, the mood improving ability is not well documented or trialled [29]. In fact users report more often feeling of wellbeing and pleasant clouding than a mood improvement. There are no data to support the antidepressant effect of cannabinoids. Younger individuals cherish Cannabinoids but it looks like the number of adverse effects is increasing with age [30]. So, in summary. Cannabinoids should not be used for their mood improving activity, especially not in older patients.

Buprenorphine

Buprenorphine (BUP) is a well know opioid analgesic drug celebrating its revival after introduction

a decade ago of transdermal BUP. Until that time the drug was available only in sublingual tablets and parenterally. BUP is a partial μ-receptor agonist and antagonist of κ-receptors and also displays affinity to other less well-known opioid receptors. It has a favourable safety profile especially in medically ill patients with poor renal and hepatic functions. With a careful and slow dose increase scheme it is safe in older people.

Its capacity to improve mood and antidepressant effects were noticed long time ago [31]. However, serious interest in the antidepressant and mood enhancing effects of BUP started from the notification that BUP is able to help patients with therapy resistant depression. The mood increasing effect is quite rapid, within few days. Antidepressant effect will be usually obvious within weeks.

It seems probable that in BUP the κ-antagonistic effects are responsible for the antidepressant effects [32]. BUP may also interact with serotoninergic system. Rapid improvement of mood has been observed in patients with treatment resistant depression. It is of particular relevance for older patients who often are unable to tolerate tricyclic antidepressants or their prognosis is too short to experience it. Not unimportant is excellent analgesic effect of this drug.

The mood improving and antidepressant effect of BUP has been studied recently [33]. In an open label study BUP was prescribed to 15 older patients troubled by treatment resistant depression. The doses ranged from 0.2–1.6 mg/day (average dose 0.4 mg/day). The depression scores (MADRS) improved within 8 weeks from 27.0 +/- 7.3 to 9.5 +/-9.5. Sharp decline in depression scores was observed in the first three weeks.

There is lack of clinical trials and for systematic reviews we should wait a bit longer.

So, in general BUP looks to be promising new antidepressant with a rapid mood improving properties. The combination with a potent analgesic effect makes it especially attractive for Palliative Care.

Discussion

Couple of drugs, well known in Palliative Care and in General Medicine exert both a mood enhancing and antidepressant effects. None of these drugs was developed for this purpose and most of these drugs are decennia old, out of patent and poorly researched. The once so important and popular congeners of amphetamine (MPH) seem to be now substituted by KET and BUP as MPH did not show convincingly the antidepressant effect in systematic reviews. KET instead scored very high in these reviews. For BUP it is probably too early to decide about.

In general antidepressant drugs act upon dopamine and serotonin and noradrenergic system. Antidepressant effects of KET use the glutaminergic pathway (NMDA receptor) and BUP used opioidergic system (κ-opioid receptor). Drugs my also, in short term influence adrenal output of cortisol. These drugs therefore can be used together with classical antidepressants or instead of them in case of drug resistance.

Cannabinoids are drugs making people happy, however not by enhancing their mood and antidepressant effect. They should not be considered here.

Neither of the drugs discussed is dangerous and contraindicated in medically ill patients. However, their use needs skilful prescribing, good information to the patient and monitoring. Boosting up dying patient who has no energy may speed up his/her death, which should be never the purpose of the treatment. I advise usually to test couple of days the drug, before they are needed. For example when the patient expects to take part in his daughter`s wedding in 6 weeks. When the test dose of for example MPH or KET appeared to improve the mood and energy level it is safe to restart this drug one day before wedding, but not using it all the time before. This may prevent tolerance development. In case of inefficacy, there is enough time to look for alternatives. Instead, BUP patch can be used all the time and is a good alternative especially when analgesia is desirable.

To make confusion even more complete Pecina et al. [34] from the renowned group of Zubieta, studied effect of placebo on major depression. In a well blinded cross-over design patients received two kinds of placebo, from which one was known to the patient as an "active" drug, another an "inactive" drug. "Active" placebo was much more effective than an inactive drug. The study, completed with MOR opioid binding studies showed that "active" placebo is associated with activation of the μ-opioid system in the brain. Many studies where candidate drugs were compared to placebo, may be flouted by this "active" placebo response. Both placebo and candidate drug may appear comparatively active which does not mean that the candidate drug is useless. Above implies that the rapid effect on mood may be the "placebo" effect of many drugs. Also, that treating patient with dignity and respect as well as paying attention to his psychological, social and spiritual issues may be effective as placebo and should be used all the time.

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