Psychotropic Medications in Palliative Care

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ABSTRACT

Psychotropic medications have had significant roles in the management of a variety of symptoms in patients living with chronic medical illness and in patients at the end of life. Intuitively, this may make sense given the considerable overlap of psychological and somatic symptoms in this population. Several reviews of the use of specific agents exist in the literature. However, a brief overview of the most commonly used psychotropic drug classes in palliative care can be helpful for a primary care provider to have as a guide to their usefulness in this population. This article reviews the use of antipsychotics, benzodiazepines, antidepressants, and psychostimulants/wakefulness agents for symptoms such as depressed mood, pain, nausea, palliative sedation, and delirium.

FOCUS POINTS

- Antipsychotics play an adjuvant role in the management of pain, nausea, and terminal sedation, but are primary agents in the management of delirium in the palliative care setting.
- Benzodiazepines play an adjuvant role in the management of pain, nausea, and delirium, but are primary agents in the management of palliative sedation.
- Psychostimulants are useful as primary antidepressants in the palliative care setting and are also helpful as adjuvant agents in the management of pain, opioid-induced sedation, and fatigue.
- Antidepressants are effective in the treatment of depression in patients with life-threatening illness, even in the palliative care setting; however, their use near the end of life is limited by the time required for the onset of beneficial effects.

INTRODUCTION

Palliative care, as both a movement and a medical subspecialty, has grown over time from a small hospice movement focusing on the care of the actively dying to a clinical specialty focusing on symptom control and provision of support to those living with chronic, life-threatening illnesses in addition to those at the end of their lives.[1] Given the burden of disease these patients face, it is perhaps not surprising that psychological symptoms such as depression, anxiety, and hopelessness are as frequent, if not more so, than other target symptoms such as pain.[1] Inversely, perhaps in part due to their proximity to mental suffering and its treatment, practitioners of this discipline have long used psychotropic medi-

cations for a variety of symptoms, both in traditional and novel ways. However, the evidence upon which some of these practices rest are variable and at times appear more historic than supported by either accumulated clinical experience or empirical evidence. The following is a brief review of some of the ways that psychotropic medications are being used in palliative care and the evidence upon which their use rests.

ANTIPSYCHOTICS

Antipsychotics have played a variety of novel roles in the treatment of the medically ill, including in the palliative care population. These drugs are divided into typical and atypical agents. Typical antipsychotics, which include haloperidol and chlorpromazine, are primarily dopamine $(D)_2$ receptor

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antagonists, blocking these receptors nonspecifically throughout the brain. This results in both their efficacy against the positive symptoms of psychotic disorders like schizophrenia, but also contributes to the associated negative sequelae such as cognitive and extrapyramidal side effects (EPS). In contrast, atypical antipsychotics are serotonin-dopamine antagonists and specifically block various serotonin and dopamine receptors simultaneously in specific regions of the brain. Through a series of complex interactions between the serotonin and dopamine regulation systems in the various dopamine pathways, atypical antipsychotics help solve the "paradox" initially posed by typical antipsychotics, allowing the treatment of both positive and negative symptoms of schizophrenia while also reducing side effects of generalized dopamine blockade, such as EPS.[2]

The result is a heterogenous group of drugs with a wide variety of potential actions that have been exploited in novel ways. Their use in the palliative care setting is an example of the flexibility with which these medications are now used, though the evidence for these uses remains variable.

Antipsychotics in Delirium

Delirium is the most common neuropsychiatric disorder reported in the terminally ill.[3-10] Various studies report prevalence rates between 20% to 88%,[3,5,6,11] with rates rising sharply as the time of death approaches.[4,9,10] Although there initially was some concern regarding the reversibility of delirium in the terminally ill, it has been increasingly clear that this is not the case and ~50% of delirium in the terminally ill cancer patients are reversible with appropriate treatment.[10] Breitbart and colleagues[3] provide a thorough review of the management of delirium in the terminally ill.

Although the mainstay of treatment for delirium still remains identifying and reversing the underlying medical cause, antipsychotics continue to play a role in the symptomatic management of delirium, particularly in the terminally ill where aggressive investigation and intervention must be weighed against comfort and quality of life.[5,12-17] A summary of routes of administration and dosages is provided in Table 1.

Typical Antipsychotics

Haloperidol has been the traditional drug of choice for the symptomatic treatment of delirium,[5] and this remains the case in the palliative care setting.[11-14,18] Typically, low doses of 0.5–2.0 mg are administered every 1–8 hours and titrated to effect,[5,6,12,14,19] with a maximum daily dose of 20 mg in most patients.[3] Lower doses are associated with better tolerability.[14] The United States Food and Drug Administration has issued a warning about the risk of QTc prolongation with the intravenous (IV) route, requiring routine electrocardiograms in non-terminal patients. Advantages of haloperidol include tolerability (at lower doses), flexibility of route (PO [by mouth], IV, SC [without food], intramuscular [IM]), and relative safety and efficacy.[3,5,11,14]

Chlorpromazine has been found to be as useful as haloperidol,[20] but is considerably more sedating, anticholinergic, and hypotensive.[3,14,21] This may make it a reasonable second-line agent for agitation that does not respond to haloperidol. Dosages for chlorpromazine range from 12.5–50.0 mg IV or SC every 4–8 hours, to a maximum of 300 mg per 24 hours for most patients.[20,22]

Methotrimeprazine is similar to chlorpromazine, and has also been found to be useful in the palliative care setting both as a neuroleptic for delirium and as an anxiolytic and analgesic that is equipotent to morphine.[22] Unfortunately, this agent is not available in the US, though it is widely used elsewhere. Dosages for methotrimeprazine range from 10–20 mg IV, IM, or SC every 4–8 hours.[20,22,23]

There is one case report[24] of zuclopenthixol acetate, an injectible typical antipsychotic with a 2–3 day efficacy window, being used successfully in delirium at the end of life. Again, this medication is not available in the US.

Atypical Antipsychotics

Of the atypical antipsychotics, risperidone, olanzapine, and quetiapine have some evidence beyond case reports of efficacy in the management of delirium.[3,12,14,25,26] Risperidone has been found to be efficacious at doses of 0.5–2.0 mg PO BID in delirious patients[14,27,28]; one small double-blind study[29] confirmed its efficacy as similar to haloperidol in delirious patients. Further evidence supports that there is reduced risk of EPS with risperidone as compared to haloperidol.[30,31]

Olanzapine has been found to be efficacious in the treatment of delirium in patients with advanced cancer without the complication of EPS,[32] and appears comparable in effect to haloperidol.[33,34] However, it may be less useful in those with hypoactive delirium, those with central nervous system (CNS) spread of cancer as the etiology of their delirium, or older patients (>70 years of age).[32] Dosing for olanzapine in delirium in the terminally ill appears to be ~2.5–20.0 mg/day PO.[14]

Quetiapine has a few open-label studies and case reports suggesting efficacy in the treatment of delirium, but sedation was a limiting factor.[35,36] Some case reports suggest that ziprasidone and aripiprazole may also be efficacious in delirium,[37-39] but the former is limited by its potential cardiac side effects[38] and the latter is still very limited in its evidence.[39,40]

Antipsychotics in Pain

Pain is a common symptom in terminally ill patients, with some suggestion that up to 50% of the terminally ill are in moderate to severe pain,[41,42] and that an estimated 25% of cancer patients die in severe pain.[41]

Although the mainstay of pain management remains opiates, antipsychotics have played an adjunct role, though the evidence for this may be limited.[43] Methotrimeprazine, as

mentioned previously, is a unique typical antipsychotic that is equianalgesic to morphine, has none of the opiod effects on gastrointestinal motility, and likely also has anti-emetic and anxiolytic effects.[41] Fluphenazine has been used successfully in combination with tricyclic antidepressants for neuropathic pain.[44]

Data for the usefulness of atypical antipsychotics is scanty, but one small prospective study[45] showed improvement of pain scale scores, reduced need to increase opiates daily, and some mild sedative effects with the adjunct use of olanzapine with opiates in cancer pain.

Antipsychotics in Nausea and Emesis

Nausea is a very common experience in both the active and palliative phases of treatment of cancer.[46-48] Although the bulk of the literature reflects treatment of nausea and emesis in patients outside of the palliative setting, a few studies do suggest that the same antipsychotics found to be useful during chemotherapy may be useful in the hospice setting.[46-50]

Phenothiazines, including chlorpromazine, methotrimeprazine, and perphenazine, have been found to be useful as anti-

emetics via D_2 blockade.[49] Prochlorperazine belongs to this family of antipsychotics, though its primary role has always been as an anti-emetic.[49] Haloperidol and droperidol have also been found to be useful for emesis via case reports and small trials,[51-53] including in the palliative population.[46,47]

Aside from prochloperazine, olanzapine has perhaps the most robust evidence for its anti-emetic effect in cancer patients both in the acute and palliative treatment phase.[48,49] It is useful both for the acute and delayed emesis of chemotherapy[54,55] as well as for intractable nausea in palliative care patients.[48,50] A proposed mechanism of action is its strong antagonism of serotonin $(5\text{-HT})_6$ and 5-HT_3, which along with its selective D_2 receptor antagonism may work at several places in the central regulation of emesis.[56]

Antipsychotics in Palliative Sedation

Palliative sedation, or terminal sedation, is a controversial practice with many definitions. Perhaps the most inclusive and general is "the use of pharmacological agents to induce unconsciousness for treatment of truly distressing and refractory symptoms in the terminally ill."[57]

TABLE 1

ANTIPSYCHOTICS USED IN DELIRIUM IN THE PALLIATIVE CARE SETTING

Drug	Titration Dose (start at lowest dose, titrate up to effect and tolerability)	Maximum Daily Dose Recommended in a 24-hour Period	Routes Available	Comments
Chlorpromazine	12.5–25.0 mg Q4–8 Hr	300 mg	Oral IM IV Subcutaneous	More sedating More anticholinergic More hypotensive Good second-line agent after haloperidol
Haloperidol	0.5–2.0 mg Q1–8 Hr	20 mg	Oral IM IV Subcutaneous	Lower doses associated with better tolerability QTc prolongation risk elevated with IV form
Methotrimeprazine	10–20 mg Q4–8 Hr	200 mg	Oral IM IV Subcutaneous	Analgesic and anxiolytic effect Not available in US
Olanzapine	2.5–20.0 mg PO Q24 Hr	20 mg	Oral (dissolving wafer available)	Comparable to haloperidol in efficacy Reduced risk of EPS May be less effective in special populations
Quetiapine	12.5–50.0 mg PO Q12 Hr	200 mg	Oral	Open-label trials suggest efficacy Sedation a limiting factor
Risperidone	0.5–2.0 mg PO Q12 Hr	6 mg	Oral (dissolving wafer available)	Comparable to haloperidol in efficacy Reduced risk of EPS
Zuclopenthixol acetate	75 mg IM Q72 Hr	NA	IM	Only one case report 48–72 hours efficacy per dose

Hr=hours; IM=intramuscular; IV=intravenous; US=United States; EPS=extrapyramidal side effects; NA=not applicable.

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Although there are no official clinical guidelines in the US, practitioners are guided by those of other nations[58] as well as some limited data.[59] There is little role for antipsychotics in palliative sedation except in the context of treating delirium. However, chlorpromazine has been used based on clinical experience, in part due to its sedating effects and relatively easy titration.[57] Its dosing and titration appears to be very similar to its use in delirium.

BENZODIAZEPINES

Benzodiazepines represent a class of anxiolytics that bind selectively to γ-aminobutyric acid receptors, resulting in several therapeutic effects (sedation, anxiolysis, muscle relaxant, anticonvulsant) and side effects (amnestic agents, ataxia, tolerance, and withdrawal).[2] Like antipsychotics, these agents have played a wide variety of roles in palliative care throughout the decades, sometimes despite limited evidence.[60,61]

Benzodiazepines in Delirium

Although historically benzodiazepines played a significant role in the treatment of delirium, there has been sufficient accumulated evidence to clarify that they are not useful as single agents in this disorder, both in non-palliative and palliative populations, and likely worsen clinical outcomes when used alone.[5,14,17,19] This appears to be largely due to their cognitive and disinhibitory effects.[14] In contrast, there is some evidence that lorazepam may have a role as adjunct therapy for hyperactive deliriums that do not respond to haloperidol alone.[14] This relatively rapid-acting and short-lived agent may be more effective in rapidly sedating agitated patients than haloperidol alone, and may also help minimize the EPS associated with haloperidol.[62] A typical dosing for this would be 1–2 mg PO/IV/IM Q1–4 hours, to be given in conjunction with regularly scheduled haloperidol.[14]

Benzodiazepines in Pain

As in delirium, benzodiazepines have had a historic role in the treatment of both acute and chronic pain, but accumulating evidence suggests that their role is likely to be adjunct at best, perhaps more related to their anxiolytic effect.[63] There is some suggestion in the literature that their anti-convulsant properties may provide some efficacy in neuropathic pain.[64] One study[65] in particular noted that alprazolam appeared to be useful as adjunct treatment for phantom limb pain in cancer patients. Similarly, clonazepam may be useful in the management of certain types of neuropathic pain in cancer patients.[66,67] Interestingly, an earlier study[63] examining the possible role of alprazolam in increasing the potency of morphine found little improvement of analgesic effect but a significant improvement in opiate-related nausea.

Benzodiazepines in Nausea and Emesis

Benzodiazepines appear to have valuable adjunct roles in nausea and emesis, largely in the treatment of anxiety and anticipatory nausea and emesis associated with chemotherapy, particularly in children.[49,68-70] One study[71] found the adjunct efficacy of lorazepam added to metoclopromide or dexamethasone regimens for chemotherapy-induced nausea to be equivalent to the adjunct efficacy of diphenhydramine added to these same regimens, but with better control of anticipatory anxiety symptoms and superior patient satisfaction in the lorazepam arm of treatment. Another study[72]—a randomized, double-blind, crossover design—showed improved efficacy of lorazepam over placebo when added as an adjunct to prochlorperazine for chemotherapy-induced nausea. However, there was no evidence found in the literature in this review to support the role of benzodiazepines as single or primary anti-emetics.[49] No clear guidelines for dosing of benzodiazepines for the treatment of emesis were found.

Benzodiazepines in Palliative Sedation

Palliative sedation is one of the few areas of palliative care where benzodiazepines are considered a mainstay of treatment.[57-59,73] Although historically, opiates and occasionally antipsychotics were utilized for this purpose, existing palliative sedation guidelines recommend midazolam as the preferred agent for this intervention.[57] The reasoning for this, supported by primarily accumulated clinical experience, is that deliberate overdose of opiates to the point of sedation often result in other unpleasant side effects, such as delirium, restlessness, sweating, myoclonus, and nausea.[57-59] Suggested dosing for midazolam in palliative sedation is 0.4 mg/hour, with dose escalation to 4.5–10.0 mg/hour.[57]

ANTIDEPRESSANTS

Similar to other psychotropic medications, antidepressants as a class can be used for the treatment of several different symptom profiles in the terminally ill. All antidepressants act through the monoamine transmitter system—impacting the release, breakdown, or reuptake of serotonin, norepinephrine or both—ultimately in delayed effect, impacting gene expression in the neurons targeted by those monoamines.[2] (Table 2 lists medications by class and clinical doses.[74])

As a class, through these similar mechanisms, these drugs can all cause to different extents neuropsychiatric side effects. Serotonin syndrome is an uncommon but potentially life-threatening toxicity from excessive serotonergic activity which clinically presents as rapid onset tremor, hyperreflexia, mental status changes, and autonomic instability. Definitive treatment is the removal of the serotonergic agent. Due to the potential serotonergic reuptake

inhibition of some opiate analgesics (including fentanyl), care should be taken.[75] These agents are also associated with akathisia—the subjective feeling of restlessness and objective motor agitation—usually in the lower limbs, bilaterally, and symmetrically.[75] This is similarly treated by removal of the causative agent.

Depression

Estimates of depression in the palliative care setting vary widely, depending on the diagnostic methods used.[76,77] Some have cited rates from 13% to 26% in the terminally ill.[78] Depression is thought to reduce quality of life and be associated with a desire for hastened death.[78-82] Yet, treatment of depression is complicated by the fact that most traditional antidepressants take several weeks to have therapeutic effect; the goal of intervention in this setting

is rapid onset of action. Thus, considerations for antidepressants are often based largely on side effect profiles, potential drug-drug interactions, and treatment goals in the setting of life expectancy.[78]

Selective Serotonin Reuptake Inhibitors

Selective serotonin reuptake inhibitors (SSRIs) are generally considered the first line for the treatment of depressive disorders in the medically ill due to the high efficacy and low side effect profile of this class. However, these medications take several weeks to show therapeutic effect. In patients with a life expectancy of several months, these medications have been shown to be helpful and effective.[83,84] Older SSRIs, fluoxetine and paroxetine, are potential inhibitors of cytochrome P450 enzymes, increasing the potential for drug-drug interactions.[64] Sertraline, citalopram, or escitalopram carry a lower risk of inhibition and thus potential drug interactions.[64]

TABLE 2

ANTIDEPRESSANTS AND PSYCHOSTIMULANTS USED IN THE PALLIATIVE CARE SETTING[74]

Drug	Starting Daily Dose mg (PO)	Therapeutic Daily Dose mg (PO)	Comments
SSRIs			
Citalopram	10	10–60	Relatively few drug interactions
Escitalopram	5–10	10–20	Relatively few drug interactions
Fluoxetine	5–10	20–60	Stimulating, long half life, higher potential for drug interactions
Paroxetine	5–10	10–60	Higher potential for drug interactions, more anticholinergic side effects
Sertraline	25	50–200	Relatively few drug interactions
Other Antidepressants			
Buproprion	75–100	150–450	Risk of seizures, useful in depression and fatigue
Mirtazapine	7.5–15	15–45	Sedating, appetite stimulant
SNRIs			
Duloxetine	20	30–60	Useful in pain and depression
Venlafaxine	37.5	75–300	Useful in pain and depression
TCAs			
Amitriptyline	10–25	50–150	Useful in pain and depression
Desipramine	10–25	50–150	Useful in pain and depression, least sedating TCA
Imipramine	10–25	50–200	Useful in pain and depression
Nortriptyline	10–25	50–150	Useful in pain and depression, least anticholinergic TCA
Psychostimulants and Wakefulness-Promoting Agents			
Dextroamphetamine	2.5–5 at 8 AM and 12 PM	50–60	Fast acting, well tolerated
Methylphenidate	2.5–5 at 8 AM and 12 PM	5–30	Fast acting, well tolerated, available in a transdermal patch
Modafinil	50–100	100–400	Fast acting, well tolerated, better cardiac tolerability

PO=by mouth; SSRIs=selective serotonin reuptake inhibitors; SNRIs=serotonin norepinephrine reuptake inhibitors; TCAs=tricyclic antidepressants.

Garcia C, Lynn R, Breitbart W. *Primary Psychiatry*. Vol 16, No 5. 2009.

Tricyclic Antidepressants

While tricyclic antidepressants (TCAs) have been shown to be effective, with sufficient time to therapeutic benefit,[84] they are less frequently used for depression alone given their anticholinergic, anti-andrenergic, and antihistaminic side effects. TCAs are more likely to be chosen for combined treatment of depression and neuropathic pain.

Serotonin Norepinephrine Reuptake Inhibitors

Serotonin norepinephrine reuptake inhibitors (SNRIs) venlafaxine and duloxetine are generally found to be well tolerated and with side effect profiles similar to SSRIs. Venlafaxine acts as an SSRI at lower doses, usually only inhibiting norepinephrine at doses >150–225 mg. Both are noted to contribute to hypertension.

Other Antidepressants

Buproprion, acting through reuptake inhibition of dopamine and some norepinephrine, is a well-tolerated antidepressant, noted to have some mild stimulating effects providing benefit to the depressed patient with prominent fatigue. It is noted to lower seizure threshold and thus is to be used with caution in patients with CNS tumors, pathology, or underlying seizure disorders. Mirtazepine, a noradrenergic and specific serotonin antidepressant, has delayed antidepressant effects through its actions at 5-HT_2 and 5-HT_3, but also causes rapid weight gain and sedation through its high affinity for H_1; these side effects can be beneficial for patients with insomnia and weight loss.[85]

Pain

One of the most difficult problems in palliative care is achievement of appropriate and sufficient palliation from pain. Many antidepressants have been shown to have analgesic effects both directly and through augmentation of opioid analgesics, independent of depressive symptoms.[86] Most studies investigate the impact of these medications in addition to opioid compounds rather than as an alternative.

Tricyclic Antidepressants

TCAs have the most robust evidence for efficacy in the treatment of pain, likely three routes: antidepressant activity, potentiation of analgesic activity,[87,88] and direct analgesic effects.[89] Amitriptyline is the most widely studied in many different types of pain, yet efficacy has been shown for imipramine, desipramine, nortriptyline, clomipramine, and doxepin.[64,87,89-91] Evidence suggests that dosing for pain control should be targeted to serum levels similar to those sought for antidepressant effect.[91]

Selective Serotonin Reuptake Inhibitors

Some trials have demonstrated efficacy of the SSRIs in the treatment of neuropathic and cancer-related pain intensity, usually equal to or approaching that of the TCAs. Fluoxetine has been demonstrated to decrease cancer-related pain intensity[84] and to act as a potentiator of morphine.[92] Similarly, paroxetine and citalopram have demonstrated efficacy in the treatment of neuropathic pain, in some cases equal to that of imipramine.[93,94] Similar evidence has yet to be specifically demonstrated for the newest of the SSRIs.

Fatigue

Fatigue is found to be a highly distressing and prevalent symptom which impacts patients' quality of life.[95] Fatigue is described as a sense of tiredness or exhaustion out of proportion to recent activity and is not responsive to rest.[96] It can be found as a side effect of opiate treatment (sedation) or associated as a symptom of depression. However, it is increasingly acknowledged as an independent complaint.[97]

Buproprion

Bupropion is often considered to be a "stimulant-like" antidepressant. It has been shown in open-label trials of the sustained release formulation, at doses between 100–300 mg, to demonstrate significant improvement in the treatment of fatigue in both depressed and non-depressed cancer patients.[98,99]

Selective Serotonin Reuptake Inhibitors

Several clinical trials of SSRIs for the treatment of fatigue have failed to show any significant effect of this drug class on fatigue alone.[100-102] Thus, SSRIs are thought only to have a role in the treatment of fatigue as a symptom of a greater depressive disorder.

PSYCHOSTIMULANTS AND WAKEFULNESS-PROMOTING AGENTS

Traditional psychostimulant medications, methylphenidate and dextroamphetamine, act predominately through release of dopamine from the presynaptic terminal, and additionally through blocking reuptake of that same dopamine.[2] These medications are generally considered to be well tolerated but do have known side effects, including agitation, insomnia, tachycardia, hypertension, and—as a result of the increased dopamine levels—psychotic symptoms.[2,103] In addition to tablet forms, methylphenidate is available in a transdermal patch.

Modafinil is a novel psychotrophic agent used to promote wakefulness in settings of excessive sleepiness; it is used for narcolepsy, obstructive sleep apnea, and shift work. While it may block some dopamine reuptake similar to the stimulants, it is thought to enhance the activity of the hypothalamic wakefulness center, promoting release of histamine, orexin, and hypocetin.[2,95] It is has less potential for dependence and fewer side effects than traditional stimulants.

Depression

Methylphenidate and dextroamphetamine have been shown in the palliative care population to be a rapid and effective treatment of depressive symptoms.[104-107] Response is anticipated within 48 hours of initiation of treatment with psychostimulants.[108] While attention must be paid to possible side effects (agitation, insomnia, tachycardia, hypertension, or rarely psychotic symptoms), these medications are noted to be very well tolerated in this population.[103]

Pain

Psychostimulants have been shown to have clear and rapid onset effects on pain. In addition to treating the excessive sedation associated with opiate treatment, both methylphenidate and dextroamphetamine have been shown in small clinical trials to potentiate the therapeutic effects of opiates.[109-112]

Fatigue

Methylphenidate has been demonstrated in both clinical trial and open-label studies to show significant improvement in the treatment of fatigue.[95,109-111] Dosing of methylphenidate has ranged from 5 mg/day–10 mg BID and as high as 30 mg total daily dose.[95,109-111,113,114] While some studies have reported patients to be largely free of troublesome side effects, others noted patients experiencing problems with insomnia and cardiovascular toxicity.

Used at low doses (200–225 mg) in chronically ill and cancer patients, modafinil has been demonstrated in open-label trials to show significant reduction in fatigue following several weeks of treatment without significant side effects.[95,115] Clinical experience suggests that this effect can be achieved quite rapidly and does not require weeks of treatment for improvement. However, randomized clinical trials are still needed to confirm these clinical observations.

CONCLUSION

Psychotropic medications have had significant roles in the management of a variety of symptoms in patients living with chronic medical illness and in patients at the end of life. This article provides a summary of the available evidence for the traditional and novel indications for antipsychotics, benzodiazepines, antidepressants, and psychostimulants. *PP*

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