

# Psychotropic drug therapy in patients in the intensive care unit – usage, adverse effects, and drug interactions: a review

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**Abstract:** Managing psychological problems in patients admitted to intensive care unit (ICU) is a big challenge, requiring pharmacological interventions. On the other hand, these patients are more prone to side effects and drug interactions associated with psychotropic drugs use. Benzodiazepines (BZDs), antidepressants, and antipsychotics are commonly used in critically ill patients. Therefore, their therapeutic effects and adverse events are discussed in this study. Different studies have shown that non-BZD drugs are preferred to BZDs for agitation and pain management, but antipsychotic agents are not recommended. Also, it is better not to start antidepressants until the patient has fully recovered. However, further investigations are required for the use of psychotropic drugs in ICUs.

**Keywords:** critical care, delirium, sedation, antipsychotics, benzodiazepines

## Introduction

Comorbidities are prevalent among critically ill patients admitted to intensive care units (ICUs), and several pharmacological and non-pharmacological treatments are usually required to manage these complications.<sup>1</sup> One of the most important issues is to manage psychiatric complications that can be accomplished by pharmacological interventions.<sup>2</sup> According to Gilbert et al study, agitation and delirium occur in 60% and 80% of patients in the ICU, respectively, and there is a direct relationship between the incidence of these complications with mortality rate, duration of mechanical ventilation, and medical costs.<sup>3</sup>

The need for appropriate sedative drugs in these patients as well as managing multiple psychiatric disturbances, including insomnia, pain, agitation, and delirium have caused unavoidable administration of a wide range of psychotropic agents in this ward.<sup>3</sup> Treating agitation and delirium even gets more difficult in patients with drug abuse who develop withdrawal symptoms on abstinence from the drug.<sup>4</sup> At the same time, psychotropic drugs should be carefully selected, since patients are at high risk of adverse drug–drug interactions. In this respect, we can mention several adverse events like arrhythmias, extrapyramidal symptoms (EPS), and even increased mortality rate due to inappropriate use of drugs or drug–drug interactions.<sup>5,6</sup>

This review article describes and compares pharmacological properties, clinical indications, and adverse drug effects of commonly used psychotropic drugs in ICUs, including benzodiazepines (BZDs), antidepressants, antipsychotics, and some other sedative agents.

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## BZDs

### Pharmacology

BZDs are generally administered for critically ill patients to manage agitation.<sup>2</sup> The proportion of gamma-Aminobutyric acid (GABA) receptors interacting with BZDs is responsible for the wide range of clinical effects: 20%, 30%–50%, and at least 60% interaction cause anxiolysis, sedation, and hypnosis, respectively.<sup>7</sup> Different pharmacological and pharmacokinetic properties of BZDs are shown in Table 1.<sup>8–11</sup>

### Clinical indications

BZDs are generally administered for critically ill patients, not only to achieve a state of deep sedation and amnesia but even in the case of a need for an anxiolytic effect. BZDs have hypnotic, anticonvulsant, and muscle relaxant effects that may be desirable in selected ICU patients.<sup>12</sup>

Midazolam and lorazepam are common BZDs that are best suited for sedation in the ICUs due to the possibility of intermittent or continuous infusion administration,

**Table 1** Pharmacodynamic and pharmacokinetic parameters of benzodiazepines

Medication	Equivalent potency (mg)	Metabolism	Elimination half-life (hours)	Onset after oral dose consumption (hours)	Comments <sup>a</sup>
Chlordiazepoxide	50	Oxidation by CYP3A4 to active metabolites (desmethyldiazepam)	30–100	1	Special attention should be paid to elderly patients, those with liver disease, persons taking other drugs interfering with BZD metabolism, or those who are poor metabolizers
Oxazepam	30	Non-CYP glucuronidation in liver to non-active metabolites	5–15	1–2	Preferred in patients with liver disease and in the elderly
Flurazepam	30	Oxidation by CYP3A4 to active metabolites (desalkylflurazepam, hydroxyethylflurazepam)	40–114 (120–160 in older adults)	0.5–1	–
Temazepam	30	Primarily non-CYP glucuronidation in liver to minimally active metabolite	8–20	0.5–1	Preferred in patients with liver disease and in the elderly
Clorazepate	15	Oxidation by CYP3A4 to active metabolites (desmethyldiazepam)	30–200	0.5–1	–
Quazepam	15	Oxidation by CYP3A4 and non-CYP metabolism in liver to active metabolites (2-Oxoquazepam, Ndesalkyl-2-oxoquazepam)	28–100 (190 in older adults)	1	–
Diazepam	10	Oxidation by CYP2C19 and CYP3A4 to active metabolites (desmethyldiazepam)	50–100 (prolonged in older adults and renal or hepatic impairment)	0.25–0.5	Special attention should be paid to elderly patients, those with liver disease, persons taking other drugs interfering with benzodiazepine metabolism, or those who are poor metabolizers
Lorazepam	1.5–2	Non-CYP glucuronidation in liver to non-active metabolites	10–20	0.5–1	Preferred in patients with liver disease and in the elderly
Alprazolam	1	Oxidation by CYP3A4 to minimally active metabolites	11–15 (16 in older adults, 20 in hepatic impairment, 22 in obesity)	1	–
Clonazepam	0.5	Oxidation and reduction by CYP3A4	18–50	0.5–1	–
Estazolam	0.3	Oxidation by CYP3A4 to minimally active metabolites	10–24	0.5–1	–
Triazolam	0.25	Oxidation by CYP3A4 to minimally active metabolites	1.5–5	0.25–0.5	–
Midazolam	–	Oxidation by CYP3A4 to non-active metabolites	1–4	0.1–0.3	–

**Notes:** <sup>a</sup>The drugs in this category have interactions with other CNS depressants such as alcohol and barbiturates and their concurrent use can lead to CNS and respiratory depression. Another significant drug interaction includes inhibitors (azole antifungals) or inducers of CYP3A4 especially in the case of diazepam and chlordiazepoxide.

**Abbreviations:** BZD, benzodiazepine; CNS, central nervous system.

and having short duration of action. Since diazepam cannot be administered by continuous infusion, it is not a suitable choice for sedation. Midazolam and diazepam are more lipid soluble than lorazepam; therefore, they have faster onset of action (2–5 minutes vs 5–20 minutes) following intravenous (IV) infusion and larger volume of distribution.<sup>13</sup> Consequently, more attention should be given to the accumulation of midazolam active metabolites, especially in obese and elderly patients by continuous infusion.<sup>14</sup>

Several studies have compared continuous infusion of midazolam vs lorazepam for sedating critically ill patients, which mostly concluded that midazolam is the preferred choice for short-term sedation, while lorazepam is suggested for long-term sedation.<sup>15,16</sup>

## Adverse effects

The incidence of adverse drug events associated with BZDs, such as respiratory suppression, reduced blood pressure, and delirium, especially in combination with opioids,<sup>17</sup> undermine the usage of these drugs for sedation.<sup>18,19</sup> According to a study, nearly 80% of critically ill patients receiving mechanical ventilation experience delirium, which costs 4–16 billion USD in the USA.<sup>20</sup> So far, different causes have been identified for delirium in ICU, including use of sedatives, especially BZDs and prolonged physical immobility.<sup>2</sup> Long-term BZD usage and their abrupt discontinuation lead to withdrawal syndrome with symptoms including agitation, anxiety, insomnia, and hyperactive delirium.<sup>21</sup>

It is worth mentioning that special care should be given to patients receiving prolonged and continuous infusion of lorazepam since there is high risk of poisoning with the solvent of these drugs, propylene glycol, which is characterized by metabolic acidosis with high anion gap and renal dysfunction.<sup>22,23</sup>

## Conclusion

Due to risk of delirium associated with BZDs and its role on prolonging ICU length of stay, the 2013 Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit suggest a non-BZD agent for sedation in critically ill patients.<sup>16</sup>

## Antipsychotics Pharmacology

There are two main types of antipsychotics according to their mechanism of action: first generation, typical or conventional antipsychotics; and second generation or atypical ones.<sup>24</sup>

First-generation antipsychotics have high affinity for dopamine (D<sub>2</sub>) receptors, while the second generation are

known as serotonin receptors antagonists (5HT<sub>2A</sub>).<sup>24</sup> Drugs in these two categories differ from one other in some pharmacologic properties, and their affinity to different receptors as shown in Table 2.<sup>25–27</sup>

## Clinical indications

Antipsychotics are mainly used to treat schizophrenia and other psychotic disorders.<sup>28</sup> Managing acute agitation and delirium in ICU is one of the most important indications of these drugs.<sup>29</sup>

Several studies on the effectiveness of Haloperidol injection to treat hyperactive delirium were published in recent years.<sup>30</sup> Due to high risk of EPS associated with haloperidol, other typical antipsychotic drugs of this category such as chlorpromazine were studied. Then, different studies were conducted on the efficacy of atypical antipsychotics including quetiapine, olanzapine, and risperidone, but results failed to show the superiority of one of these drugs in treating delirium.<sup>31,32</sup>

For instance, in one study that evaluated the effect of low-dose haloperidol in comparison with atypical antipsychotics, such as olanzapine and risperidone, no significant difference was observed. However, the incidence of adverse effects including EPS was higher in patients receiving haloperidol. Although atypical antipsychotic agents are not superior to haloperidol, it is suggested to administer these drugs due to their less adverse effects. This is suggested for patients receiving high-dose haloperidol (>4.5 mg/day) for treating delirium, but we should also consider that these drugs are more expensive.<sup>31</sup> In recent years, studies on control and prevention of delirium in critically ill patients could not prove the efficacy and safety of antipsychotic agents.

Antipsychotics treatment duration and appropriate time to discontinue these drugs were other important issues, considered in some studies. For example, in the Modifying the Incidence of Delirium trial, all the patients received their antipsychotic agents, and these drugs were discontinued when patients were delirium-free for 48 hours, but this study did not find a direct relationship between treatment with antipsychotics and duration of delirium.<sup>31</sup> The significance of this issue is lack of timely drug discontinuation and even if patient is discharged with these drugs, it would lead to drug interaction due to unnecessary antipsychotic agents in drug regimen of polypharmacy patients, as well as increasing medical costs. Jasiak et al study estimated that cost of continued unnecessary treatment with atypical antipsychotic medication was 2,255.35 USD.<sup>33</sup> In another study, it was shown that patients receiving BZDs for a longer period in ICU were more likely to be discharged with a new

Table 2 Characteristics and properties of antipsychotics

Medication	Equivalent dose (mg)	Metabolism	Elimination half-life (hours)	Onset after oral dose consumption	Comments <sup>a</sup>
<b>FGAs</b>					
<b>Low potency</b>					
Chlorpromazine	100	Mainly CYP2D6; also, other CYPs and UGT glucuronidation to active and inactive metabolites	24–30	30–60 minutes	Variable oral absorption; high sedation, anticholinergic side effects, and orthostatic hypotension especially in older adults and mechanically ill patients
Thioridazine	100	Mainly CYP2D6; also, other CYPs to active (mesoridazine) and inactive metabolites	Parent drug: 4–10 Active metabolites: 21–25		Dose-dependent retinitis pigmentosa; very high risk of QTc prolongation; prolactin elevation; high sedation, anticholinergic side effects, and orthostatic hypotension
<b>Mild potency</b>					
Loxapine	10	CYP1A2, CYP2D6, and CYP3A4 and UGT glucuronidation to active and inactive metabolites	Parent drug: 6–8 Active metabolites: 12	Within 0.5 hours	–
Perphenazine	8–10	Mainly CYP2D6; also, CYP3A4 and other CYPs to active and inactive metabolites	Parent drug: 9–12 Active metabolites: 10–19	2–4 weeks	Variable bioavailability (60%–80%); similar tolerability and efficacy to some SGAs in higher daily doses
<b>High potency</b>					
Trifluperazine	5	Mainly CYP1A2; also, other CYPs to active and inactive metabolites	Parent drug: 3–12 Active metabolites: 22	2–4 weeks (control of agitation, aggression, hostility) Within 1 week (control of psychotic symptoms)	Variable bioavailability; high EPS and TD
Thiothixene	4	CYP1A2 and other CYPs	34	–	Variable oral absorption, high EPS and TD
Fluphenazine	2	CYP2D6	14–33	–	Highly variable oral absorption, high EPS and TD
Haloperidol	2	Mainly CYP2D6; also, CYP3A4 and UGT glucuronidation; some metabolites potentially active or toxic	18–20	–	High EPS and TD; prolactin elevation; QTc prolongation
Pimozide	1	CYP1A2, CYP2D6, CYP3A4, and others	55; 150 in CYP2D6 poor metabolizers	Within 1 week	Variable bioavailability due to extensive hepatic first-pass metabolism; high EPS and TD
<b>SGAs</b>					
Quetiapine	75	CYP3A4	6–12	–	Least likely to induce drug-induced parkinsonism; QTc prolongation; monitor patients routinely for glucose dysregulation, weight gain, and hyperlipidemia; increased likelihood of CVAs and TIAs in elderly patients
Ziprasidone	60	CYP3A4	7	5–5.5 hours in children; 6–8 hours in adults	High risk of QTc prolongation

Clozapine	50	CYP1A2, CYP3A4, other CYPs, and UGT glucuronidation	8–12	Within 1 week (sedation); 6–12 weeks (antipsychotic effects)	Potent muscarinic receptor antagonists; the most frequent dose limiting factor is hypotension; one of the most metabolically problematic agents (glucose dysregulation, weight gain, and hyperlipidemia); dose-related tachycardia; sialorrhea; black box warnings: agranulocytosis, seizures, myocarditis, other adverse cardiovascular and respiratory effects, and increased mortality in elderly patients with dementia-related psychosis
Aripiprazole	7.5	CYP2D6 and CYP3A4 to active and inactive metabolites	75–94	1–3 weeks	Partial D2 receptor agonist; so, better to take in the morning as it may be activating in some patients; decreases serum prolactin and triglycerides; low risk of weight gain, dyslipidemia, and QTc prolongation; partial D3 agonist and may induce an increase in risky, reward-based behaviors, such as gambling
Olanzapine	5	CYP1A2, CYP2D6, and UGT glucuronidation	21–54	Within 1–2 weeks (control of aggression, agitation, insomnia); 3–6 weeks (control of mania and positive psychotic symptoms)	Potent muscarinic receptor antagonists; high risk of glucose dysregulation, weight gain, and hyperlipidemia
Paliperidone	3	Mainly excreted unchanged in urine; also, limited CYP2D6 and CYP3A4	23	–	Dose reduction in renal insufficiency is necessary
Risperidone	2	CYP2D6 to active (paliperidone) and inactive metabolites; P-gp substrate	3–20	–	Prolactin elevation; weight gain; orthostatic hypotension; high EPS and TD
Asenapine	–	CYP1A2 and UGT glucuronidation	24	–	–
Lurasidone	–	CYP3A4 to active and inactive metabolites	18–37	–	Absorption increases when taken with a meal
Iloperidone	–	CYP2D6, CYP3A4, and other CYPs to active and inactive metabolites	18–33	–	Significant orthostatic hypotension

**Notes:** <sup>†</sup>Most antipsychotics are metabolized by CYP450 isoenzymes, so the inhibitors (fluvoxamine, fluoxetine, paroxetine, bupropion, and ciprofloxacin) or inducers of these isoenzymes (carbamazepine, phenytoin, and cigarette smoke) can change the antipsychotic serum levels. These interactions are more significant for agents such as clozapine. Also administering medications with overlapping side effects such as cardiac, sedative, anticholinergic, or metabolic risks should be avoided.

**Abbreviations:** FGA, first-generation antipsychotic; UGT, UDP-glucuronosyltransferase; SGA, second-generation antipsychotic; EPS, extrapyramidal symptoms; TD, tardive dyskinesia; CVAs, cerebrovascular accidents; TIAs, transient ischemic attacks; P-gp, P-glycoprotein; QTc, corrected QT interval.

antipsychotic agent, which could cause higher rate of adverse drug reactions (ADRs) in polypharmacy patients.<sup>34</sup>

## Adverse effects

First-generation drugs are more likely to produce EPS due to more potent inhibition of D<sub>2</sub> receptors. The EPS side effects mostly occur when the patient is taking high dosage of typical antipsychotics. Those symptoms include akathisia, acute dystonic reaction (more often in young male patients), parkinsonism (more in old females), and tardive dyskinesia (in patients who receive first-generation antipsychotic for a long period of time).<sup>35</sup> Also, low potent first-generation drugs such as chlorpromazine and thioridazine have more anticholinergic effects than the high potent ones including haloperidol, fluphenazine, and trifluoperazine. Accordingly, clozapine and olanzapine as second-generation drugs have the most anticholinergic and sedative effects.<sup>36</sup> Hence, special attention should be given to these pharmacologic differences and side effects when selecting a drug from this category.

In a prospective study in 2016, it was observed that 18% of patients with delirium who were receiving antipsychotics experienced ADRs, half of which were severe or harmful including corrected QT interval (QTc) prolongation (10%), drowsiness (20%), ventricular tachycardia (10%), fever (10%), and neutropenia (10%). Severe and harmful adverse reactions were mainly observed in receiving first-generation antipsychotic drugs.<sup>6</sup>

Also, in one study that evaluated the incidence of QTc prolongation in critically ill patients, haloperidol, amiodarone, and levofloxacin were among the main causes of QTc prolongation.<sup>5</sup> Furthermore, the most common drug interactions leading to QTc prolongation, haloperidol, was among the first five frequently prescribed drugs in patients.<sup>3</sup>

One concerning issue is the incidence of torsades de pointes in patients receiving antipsychotics, especially patients with risk factors such as hypokalemia and hypomagnesemia.<sup>37</sup> However, this risk was higher in patients receiving IV haloperidol; some torsades de point cases were reported due to the use of atypical antipsychotics, such as ziprasidone and risperidone.<sup>38</sup> Even though there are not ample amount of evidence, related mortality and morbidity are significant and should be considered when administering these drugs.

The incidence of ADRs and drug interactions with typical antipsychotics, particularly haloperidol which is commonly administered in the ICUs, led to use of atypical antipsychotics.

A multicenter prospective study was conducted to evaluate the efficacy and safety of treatment with quetiapine in critically ill patients. Shorter delirium duration, less agitation, and reduced

need to haloperidol was observed among patients receiving quetiapine (50 mg by mouth (PO) every 12 hours which was increased every 24 hours up to 200 mg every 12 hours) in comparison with placebo, but there was no significant difference in the incidence of QTc prolongation and EPS.<sup>32</sup>

In one study, acute hyperglycemia independent from other glucose elevation factors in patients treated with quetiapine was considered as an adverse effect.<sup>39</sup>

## Conclusion

Although typical antipsychotics such as haloperidol have been extensively used to prevent delirium, it seems that the data for using atypical antipsychotic agents are promising. In summary, according to what was mentioned so far in terms of efficacy and safety of antipsychotics in clinical practice guideline for managing delirium in ICUs (2013), atypical antipsychotics are not recommended to prevent delirium (level of recommendation: -2C).<sup>16</sup>

## Antidepressants Pharmacology

Selective serotonin reuptake inhibitors (SSRIs) selectively block the reuptake of serotonin at presynaptic neuronal junction, while selective serotonin-norepinephrine reuptake inhibitors (SNRIs) inhibit the reuptake of both norepinephrine and serotonin.<sup>40</sup> Different pharmacologic and pharmacokinetic properties of these drugs are shown in Table 3.<sup>27,41-45</sup>

## Clinical indications

Antidepressants have been approved for some conditions such as depression, anxiety, neuropathic pains, and fibromyalgia; their use is often limited in ICU.<sup>40</sup> Nearly 17% of patients in ICU have SSRI or SNRI in their medication history list on admission.<sup>46</sup> Therefore, with regard to the increasing consumption of these drugs, continuation of taking these medications during admission is an important issue. Abrupt discontinuation of SSRI/SNRI drugs can lead to withdrawal syndrome in critically ill patients, attenuate the patient's psychiatric condition like depression, and have a negative impact on the patient's recovery in critically ill settings.<sup>47</sup> Several points should be considered regarding continuation or initiating of SSRI/SNRI therapy which are described in the next section.

## Adverse effects

Due to the effect of serotonin inhibitors on platelet functions, special attention should be given to upper gastrointestinal and preoperative bleeding.<sup>48,49</sup> Risk of bleeding increases,

**Table 3** Different characteristics and properties of antidepressants

Medication	Metabolism	Elimination half-life (hours)	Onset after oral dose consumption	Comments <sup>a</sup>
<b>SSRIs</b>				
Citalopram	CYP3A4, CYP2D6, and CYP2C19 to weakly active metabolites (desmethylcitalopram, didesmethylcitalopram)	33–35	1–4 weeks	The highest protein binding among SSRIs; dose-related QTc prolongation
Escitalopram	CYP3A4, CYP2D6, and CYP2C19 to weakly active metabolites (S-desmethylcitalopram, S-didesmethylcitalopram)	27–32	Within a week	The least protein binding among SSRIs (56%)
Fluoxetine	CYP3A4, CYP2D6, and CYP2C9 to active metabolites (norfluoxetine)	Parent drug: 24–144; active metabolite: 96–384	Within a week	Causes a decrease in appetite; activating agent; longest half-life among SSRIs
Paroxetine	CYP2D6 to non-active metabolites	21–24	Within a week	A weak anticholinergic agent; very high risk of sexual dysfunction; weight gain
Sertraline	CYP3A4, CYP2D6, and CYP2C19 to weakly active metabolites (desmethylsertraline)	26	Within a week	More GI disturbances including diarrhea than other SSRIs; variable oral bioavailability
<b>SNRIs</b>				
Duloxetine	CYP1A2 and CYP2D6 to inactive metabolites	12 (8–17)	–	Should not be used in patients with substantial alcohol use or evidence of chronic liver disease due to an increase in LFTs
Venlafaxine	CYP2D6 to active metabolite (O-desmethylvenlafaxine) and inactive metabolites (N-desmethylvenlafaxine, N,O-didesmethylvenlafaxine)	Parent drug: 4; active metabolite: 11	–	Dose-related increase in BP and heart rate
Desvenlafaxine	Mainly via hepatic conjugation; also, oxidation by CYP3A4	10–11	–	–
Levomilnacipran	Hepatic to inactive metabolites	12	–	More potent effects on NE as compared to its 5-HT reuptake; the greatest risk of increasing BP among SNRIs

**Notes:** <sup>a</sup>Most SSRIs are inhibitors of the CYP/CYP450 isoenzymes and can alter the blood levels of other medications. Among them, sertraline, citalopram, and escitalopram have the minimal effect on CYP450 enzyme system. Fluoxetine and paroxetine have the highest impact on CYP2D6 (interaction with tamoxifen), and fluvoxamine is potent inhibitor of CYP1A2. Among SNRIs, only duloxetine is a moderately potent inhibitor of CYP2D6 and the others do not have significant effect on CYP/CYP450 isoenzymes. SNRIs should not be used in patients who have received MAOIs in previous 2 weeks due to the risk of serotonin syndrome.

**Abbreviations:** SSRI, selective serotonin reuptake inhibitor; GI, gastrointestinal; SNRI, serotonin–norepinephrine reuptake inhibitor; LFT, liver function test; BP, blood pressure; QTc, corrected QT interval; NE, norepinephrine; MAOIs, monoamine oxidase inhibitors; HT, hydroxytryptamine.

especially when used concurrently with antiplatelet agents and common anticoagulants like aspirin or warfarin.<sup>49</sup> On the other hand, drugs affecting serotonin reuptake are considered as a factor causing or exacerbating delirium in critically ill patients.<sup>50</sup>

Serotonin syndrome is one of the important ADRs associated with the use of drugs affecting serotonin reuptake, caused by excessive activation of postsynaptic serotonin receptors.<sup>51</sup> This syndrome's manifestation, such as altered mental status, neuromuscular irritability and autonomic instability are due to its impact on central nervous system (CNS).<sup>52</sup> In one study, the incidence of this adverse reaction in ICU was estimated to be 39%.<sup>53</sup> This syndrome can occur due to overdose with single serotonin agents, but most of the severe cases are because of interaction between two or more

drugs increasing serotonin transmission. Drugs that so have shown to interact with SSRI/SNRI agents and can cause serotonin syndrome include linezolid, meperidine, tramadol, and dextromethorphan.<sup>54,55</sup>

Another risk in using SSRI in ICUs is higher risk of vasospasm followed by aneurysmal subarachnoid hemorrhage, and current use of statins can increase the risk of this adverse effect.<sup>56</sup>

Other adverse effect of SNRI/SSRI use in ICU includes fever, known as drug fever.<sup>57</sup>

## Conclusion

The response to the question whether SSRI/SNRI agents should be discontinued, tapered off, or be continued in critically ill patients requires further investigations. Kelly et al

study indicated that it is better to hold these drugs in acutely critically ill patients and when they become stable, start them again after psychiatric consultation.<sup>46</sup>

## Alpha2 agonists

### Pharmacology

Alpha2 adrenergic stimulation leads to adenylate cyclase inhibition and subsequently a decrease in cyclic adenosine monophosphate (cAMP) production.<sup>58</sup> Reduction of cAMP level and efflux of potassium through an activated channel causes hyperpolarization of excitable membranes that prevents neurons activation. Alpha2 adrenergic stimulation prevents calcium from entering the nerve terminals, responsible for exertion of a very powerful inhibition of adrenergic tone.<sup>59</sup>

Dexmedetomidine, clonidine, methyl dopa, and guanabenz are examples of alpha2 receptor agonists. Among them, dexmedetomidine is commonly used for conscious sedation in critically ill patients. The characteristics of these drugs are shown in Table 4.<sup>16,26,60,61</sup>

### Clinical indications

Alpha2 receptor agonist indication mainly depend on their effects in CNS. These effects include sedation, analgesia, anesthetic sparing, and sympatholytic properties.<sup>62</sup>

Clonidine is an imidazoline compound, which is a selective alpha-2-agonist with selective ratio of 200/1 for alpha2/alpha1.<sup>63</sup> This drug is used in conditions such as high blood pressure, migraine, menopause flushing, and alcohol withdrawal syndrome.<sup>64,65</sup> Clonidine has dose-related effects such as sedation, anxiolysis, and analgesia and can reduce the need for other anesthetic drugs and opioids in ICUs.<sup>66</sup>

Clonidine is an ideal agent for sedation in ICUs due to its minimal respiratory suppression and insignificant effects on respiratory rate, PaCO<sub>2</sub>, and SpO<sub>2</sub>.<sup>67,68</sup> Nowadays in Europe, clonidine is one of the most popular drugs for sedation in ICUs.<sup>69</sup>

Dexmedetomidine is a newer and more selective alpha2 receptor agonist (with eight times more affinity to  $\alpha_2$  receptors than clonidine) with sympatholytic, sedative, analgesic (opioid sparing), anxiolytic, and anesthetic drug-sparing effects and, of note, without respiratory depression.<sup>70-72</sup> In clinical trials on dexmedetomidine, this drug showed to reduce the duration of mechanical ventilation in comparison with midazolam.<sup>73</sup> Also, patients receiving dexmedetomidine were aroused more easily and had lower rates of postoperative delirium than those using propofol and midazolam.<sup>74</sup>

Dexmedetomidine is only used as IV infusion. All patients should be under continuous cardiac monitoring during treatment period. Also, non-mechanically ventilated patients should be monitored for respiration.<sup>75</sup>

Dexmedetomidine has a half-life of 2 hours. Its maximum dose is 1.4  $\mu\text{g}/\text{kg}\cdot\text{hour}$ , and due to transient hypertension, loading dose is not recommended.<sup>75</sup> In the USA, dexmedetomidine is approved for infusion of up to 1 day only in mechanically ventilated patients. It is the only approved drug in the USA for inducing sedation in non-mechanically ventilated patients.<sup>76</sup>

According to a meta-analysis conducted in 2014, dexmedetomidine was associated with reduced incidence of delirium, agitation, confusion as well as shorter ICU stay, and extubation in comparison with other sedative agents.<sup>77</sup>

Considering its lack of effect on respiratory drive, being only available as IV formulation, requiring cardiovascular

**Table 4** The characteristics and properties of alpha2 agonists

Medication	Metabolism	Elimination half-life	Onset of action after consumption (minutes)	Comments <sup>a</sup>
Dexmedetomidine	CYP2A6 and glucuronidation	3 hours (prolonged in hepatic impairment)	5–15 (5–10 and 15 with and without loading dose administration)	Potentially significant hypotension and bradycardia or hypertension that do not resolve quickly upon abrupt discontinuation which occur more commonly in patients with cardiovascular instability or hypovolemia; rapid administration of loading dose may be associated with cardiovascular instability, tachycardia, bradycardia, or heart-block; does not induce the deep sedation needed for neuromuscular blockade
Clonidine	Hepatic metabolism to inactive metabolites	12–16 hours (41 hours in renal impairment)	10	Causes bradycardia, hypotension, and xerostomia; use with caution in patients with cardiovascular and cerebrovascular diseases; CNS depressant

**Notes:** <sup>a</sup>Drugs that alter the blood pressure level can affect hypertensive or hypotensive effect of alpha2 agonists. Tricyclic antidepressants can desensitize alpha2 adrenoreceptors and should be stopped 3 weeks prior to use of these two drugs.

**Abbreviation:** CNS, central nervous system.



monitoring during infusion period and the high cost, researchers have attempted to develop strategies to switch from dexmedetomidine to enteral clonidine.<sup>78,79</sup> In this regard, an observational pilot study was conducted on critically ill patients who had sustained agitation and were treated with dexmedetomidine to reach a Sedation Agitation Scale (SAS) score of 3–4.

If patients showed appropriate response (SAS: 3–4) between 12 and 24 hours, while being hemodynamic stable, dexmedetomidine would be switched to clonidine (0.2–0.5 mg every 6 hours PO). Finally, it was observed that the efficacy and safety of clonidine for sedation induction was not statistically different from dexmedetomidine, but this change from dexmedetomidine to oral clonidine could reduce drug cost 819–2,338 USD per patient within the 3 months of study period.<sup>80</sup>

## Adverse effects

Bradycardia, hypotension, and xerostomia are considered as side effects of clonidine.<sup>81</sup> These side effects, rebound hypertension and tachycardia following sudden cessation of clonidine after prolonged usage, have led to the development of other alpha2 agonists, such as dexmedetomidine.<sup>82</sup> Hence, according to the latest guidelines in ICU settings, clonidine is considered as one of the agents for treating delirium and as second-line agent for inducing sedation.<sup>16</sup>

Dexmedetomidine causes dose-dependent bradycardia, hypertension, or hypotension. These effects are clinically relevant in those patients in whom hemodynamic conditions rely on augmented sympathetic stimulation and vasoconstriction, for example, those with fixed stroke volume and hypovolemic status, on rate-reducing drugs (beta blockers or digitalis).<sup>83</sup> These side effects can be omitted by omitting loading dose or slowly incrementing infusion rate.

## Conclusion

As mentioned before, according to Pain, Agitation, and Delirium management guideline which was released in 2013, it is recommended to use non-BZD strategies, such as dexmedetomidine instead of BZDs to prevent delirium. Also, dexmedetomidine is considered as an agent that can prevent delirium in ICU setting (level of recommendation: +2B).<sup>16</sup>

## Others

Propofol and ketamine are sedative hypnotic drugs used for sedation in ICUs, but their usage is limited.<sup>84</sup>

## Propofol Pharmacology

It is a GABAergic IV anesthetic used to sedate the agitated critically ill patients.<sup>85</sup> Propofol inhibits acetylcholine release in the hippocampus and prefrontal cortex through its effect on GABA receptors. It also acts through  $\alpha 2$ -adrenoreceptor and inhibits the N-Methyl-D-aspartate (NMDA) subtype of glutamate receptor. Propofol is not an analgesic agent. It has a potent antiemetic action, probably due to a decrease in serotonin levels through its action on GABA receptors in the area postrema.<sup>86–89</sup> Table 5 shows pharmacokinetic and pharmacologic characteristics of propofol and ketamine.<sup>90,91</sup>

## Clinical indications

Propofol is considered as a drug of choice due to its rapid onset, rapid awakening, and antiemetic effects.<sup>92</sup> In recent years, usage of this agent to induce and maintain sedation in critically ill patients has been controversial.

Many studies have evaluated and compared propofol with other sedative agents in terms of efficacy, safety, and inducing sedation. For example, in a retrospective study that compared propofol-based vs dexmedetomidine-based

**Table 5** Pharmacodynamic and pharmacokinetic properties of propofol and ketamine

Medication	Metabolism	Elimination half-life (hours)	Onset after oral dose consumption	Comments <sup>a</sup>
Propofol	Hepatic mainly via CYP2B6 to water-soluble sulfate and glucuronide conjugates; also, via CYP1A2, CYP2A6, CYP2C19, CYP2C9, CYP2D6, CYP2E1, and CYP3A4	4–7	1–2 minutes	Cardiovascular and respiratory depression (propofol-related infusion syndrome); hypotensive agent; contraindicated in patients with egg allergy
Ketamine	Hepatic via CYP2B6, CYP2C9, and CYP3A4 to active (norketamine) and non-active metabolites; also, via hepatic conjugation	1–2	30 seconds IV; 3–4 minutes IM	Increased airway secretions and laryngospasm; elevated IOP and ICP; emergence reactions, CNS depressant, sympathetic stimulator (increases HR and BP); psychotomimetic effects (hallucinations and nightmares)

**Notes:** <sup>a</sup>Special care should be taken when administering propofol with alfentanil (due to risk of opisthotonus and/or grand mal seizures), CNS, and respiratory depressants (opioid narcotics, sedatives). Ketamine can worsen cardiovascular toxicity of cocaine and TCAs.

**Abbreviations:** IV, intravenous; IM, intramuscular; IOP, intraocular pressure; ICP, intracranial pressure; HR, heart rate; BP, blood pressure; CNS, central nervous system.

sedation in cardiac surgery patients, they concluded that patients sedated with dexmedetomidine were extubated faster than patients receiving propofol. Also, the length of hospital stay in dexmedetomidine-based group was shorter than propofol-based group.<sup>93</sup> However, according to one review article published in the *New England Journal of Medicine*,<sup>94</sup> there was no difference in the duration of mechanical ventilation and ICU stay between patients receiving propofol and dexmedetomidine.

In another meta-analysis study that evaluated the efficacy and harmful effect of propofol vs midazolam, they concluded that propofol was superior to midazolam for sedating mechanically ventilated critically ill patients.<sup>95</sup>

In a multicenter ICU database analysis that evaluated 3,000 patients admitted to an ICU, lower rate of mortality, shorter duration of mechanical ventilation, and earlier discharge were observed in patients receiving propofol infusions in comparison with those using lorazepam or midazolam.<sup>96</sup> However, it seems that more data from comparative trials with current sedation guideline studies are required to confirm these results.

## Adverse effects

The vasodilatory effect of this drug is responsible for severe hypotension in some patients, especially those with cardiac dysfunction or hemodynamic instability.<sup>97</sup> When bolus injection of this drug is required, it should be infused according to the patient's blood pressure.<sup>98</sup> The incidence of hypertriglyceridemia is rare, but it mostly occurs with high propofol continuous infusion rate or when the patient is receiving parenteral nutrition formulations containing lipid.<sup>99</sup> Especially this side effect should be considered in patients who are older and have a longer ICU stay which can be further complicated by the development of pancreatitis.<sup>100</sup>

Propofol-related infusion syndrome (PRIS) is an unusual and serious adverse effect of long-term propofol infusion. Its clinical symptoms include acute refractory bradycardia progressing to asystole, metabolic acidosis rhabdomyolysis of both skeletal and cardiac muscle, hyperlipidemia, and enlarged or fatty liver.<sup>101</sup> It usually occurs with doses more than 67  $\mu\text{g}/\text{kg}\cdot\text{min}$  and infusions longer than 48 hours.<sup>102</sup> Concurrent use of glucocorticoids, catecholamine infusion, high fat, and low carbohydrate intake are other risk factors for developing PRIS.<sup>103</sup> The incidence of PRIS is <1%, but if it occurs, it has high mortality rate. Consequently, it is suggested to check triglyceride levels, serum lactate, and creatine kinase in patients receiving propofol. Hence, discontinuation of propofol and supportive care can treat PRIS.<sup>104</sup>

## Conclusion

Altogether, the results of conducted studies on propofol show that this agent is favorable when rapid sedation and rapid awakening are desired; stopping the infusion can reverse the sedative effects, usually within 1 hour and often within 15 minutes but should pay attention to the patient's hemodynamic condition and the incidence of adverse events.<sup>82,92</sup>

## Ketamine Pharmacology

Ketamine is an IV anesthetic which has been used since 1975 due to its different pharmacological properties, such as sedation, somatic analgesia, sympathetic nervous system stimulation, and bronchodilation.<sup>105</sup> Ketamine is a phencyclidine derivative that competitively inhibits NMDA as well as sigma opioid receptors.<sup>106</sup>

Ketamine passes through blood–brain barrier very swiftly and its onset and duration are close to 1 and 10–15 minutes, respectively.<sup>107</sup>

## Clinical indications

Induction of dissociative anesthesia in which the patient is nonresponsive to nociceptive stimulators, while the eyes are open and reflexes remain, is considered as a unique characteristic of ketamine.<sup>107</sup> Due to sympathomimetic hemodynamic effects that can lead to vasoconstriction and positive inotropic actions, ketamine is an attractive choice for inducing sedation in sepsis.<sup>108</sup> Thus, it seems to be a safer choice than midazolam, etomidate, and propofol for inducing sedation in septic shock among critically ill patients.<sup>109</sup> Also, due to its bronchodilatory property, it is an appropriate choice for inducing sedation in asthma attacks and bronchoconstriction.<sup>110</sup> Continuous infusion of ketamine and propofol can provide adequate and safe sedation for short time (<24 hours) in critically ill patients.<sup>111</sup>

In one study, it was stated that ketamine is a favorable choice in patients with intracranial hypertension who are under mechanical ventilation,<sup>112</sup> but today it is believed that in patients with increased intracranial pressure (ICP), the depth of sedation is more important than selecting a sedative agent for managing these patients.<sup>113</sup> In addition, it has been observed that low dose of ketamine (60–120  $\mu\text{g}/\text{kg}\cdot\text{hour}$ ) with BZDs or particularly opioids can have beneficial effects for critically ill patients. The reason is as follows: the necessary effects of ketamine occur in lower doses in comparison with psychotropic effects. Thus, appropriate analgesic effects occur in lower doses without being concerned about its psychiatric adverse events, which is observed less frequently

with BZDs and opioids.<sup>114</sup> Unlike opioids that cause ileus, ketamine does not inhibit bowel motility, thus constipation occurs less frequently.<sup>115</sup> Additionally, ketamine reduces opioid-induced hyperalgesia; hence, the patients require less dose of opioids.<sup>116</sup>

## Adverse effects

Increase in saliva secretion is an adverse effect of ketamine, which might lead to laryngospasm, requiring suction or premedication with atropine in patients under ventilation.<sup>117</sup> However, psychoactive effects of ketamine (vivid hallucination, confusion, and delirium) have threatened its status as a safe sedative agent.<sup>118</sup> On the other hand, due to the effect of ketamine on intraocular pressure, it is recommended to limit its usage in patients with open glaucoma.<sup>119</sup>

## Conclusion

According to the above-mentioned studies, ketamine is now considered as an agent for rapid sequence intubation (RSI), and we need more clinical studies to evaluate its safety in critically ill patients.

## Summary

Controlling psychiatric problems in critically ill patients is an important issue. Their poor management can lead to attenuation of patients' settings and affect their recovery. On the other hand, using psychotropic drugs might increase the risk of drug–drug interactions or ADRs. Therefore, selecting appropriate psychotropic drugs for critically ill patients is a crucial challenge.

Further studies are required on the efficacy and safety of psychotropic drugs, but the results of several studies have shown that it is better to use non-BZD drugs instead of BZDs to control agitation and pain. In this regard, cost is an important factor. The use of BZDs should be limited (as well as barbiturate) in patients with head trauma, intracranial hemorrhages, or epilepsy to prevent increase of ICP. If it is necessary to use BZDs, they should be given in the lowest possible dose for the shortest duration to prevent adverse effects.

Alpha2 agonists, such as dexmedetomidine are preferred over BZDs for inducing sedation, because they can prevent delirium in ICU setting.

Propofol has a rapid onset of action and recovery, but the incidence of adverse events is high. Ketamine is a favorable choice for RSI; however, it causes psychological complications in a dose-dependent manner.

Antipsychotic agents, either first generation or second generation, are not recommended, but it seems that atypical

antipsychotics are associated with less ADRs when used to treat delirium. Nonetheless, special care should be given to patients prone to arrhythmias (ie, patients with history of arrhythmias and patients receiving proarrhythmogenic agent).

The use of antidepressants is often limited in ICU, and their administration is only recommended when the patients are in stable condition.

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## Author contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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