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Ann. Acad. Med. Siles. (online) 2026; 80: 113–123
eISSN 1734-025X
DOI: 10.18794/aams/211947
www.annales.sum.edu.pl

PRACA POGLĄDOWA
REVIEW

The dopamine pathogenesis of delirium: A review of dopaminergic therapeutic approaches in the treatment and prevention of delirium

Dopaminowa patogeneza majaczenia – przegląd dopaminergicznych metod terapeutycznych w leczeniu i prewencji delirium

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ABSTRACT

Delirium is a neuropsychiatric disorder whose multivector pathogenesis is not clear. The current state of knowledge favors the system integration failure hypothesis (SIFH), in which crucial roles are played by central nervous system structures involved in dopaminergic transmission. The aim of the search is to find therapeutic approaches that target alterations of dopaminergic transmission. Methylphenidate was shown to improve cognitive function in advanced cancer patients with hypoactive delirium, as demonstrated by an increase in mean scores on the Mini-Mental State Examination (MMSE) from 20.9 to 27.8. Yokukansan did not significantly affect the overall risk of postoperative delirium following oncologic surgery; however, in patients aged 75 years or older, it reduced the incidence of delirium with agitation (21.4% vs. 71%). Aripiprazole showed no difference compared to other antipsychotics in delirium resolution efficacy without distinguishing into subtypes, but had fewer side effects. In hypoactive delirium, it showed both a higher rate of resolution and improvement in the Memorial Delirium Assessment Scale (MDAS) score compared to haloperidol. Intervention with dopaminergic drugs has shown a superior effect in treating the hypoactive subtype with coexisting terminal cancer, while all therapeutic approaches have shown efficacy compared to a placebo in treating and preventing delirium episodes.

KEYWORDS

dopamine, delirium, aripiprazole, methylphenidate, yokukansan

Received: 10.07.2025 **Revised:** 07.10.2025 **Accepted:** 11.10.2025 **Published online:** 12.03.2026

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Publisher: Medical University of Silesia, Katowice, Poland

STRESZCZENIE

Delirium (majaczenie) jest zaburzeniem neuropsychiatrycznym, którego wielowektorowa patogeneza nie jest jeszcze w pełni wyjaśniona. Obecny stan wiedzy przemawia za hipotezą nieprawidłowego funkcjonowania integracji układów (*system integration failure hypothesis* – SIFH), w której kluczową rolę odgrywają struktury ośrodkowego układu nerwowego zaangażowane w przekaźnictwo dopaminergiczne. Celem przeglądu jest analiza działania oraz skuteczności metod terapeutycznych ukierunkowanych na modulacje transmisji dopaminergicznej. Wykazano, że metylofenidat poprawia funkcje poznawcze u pacjentów z zaawansowanym nowotworem i majaczeniem hipoaktywnym, o czym świadczy wzrost średnich wyników w skali Mini-Mental State Examination (MMSE) z 20,9 do 27,8. Yokukansan nie wpłynął znacząco na ogólne ryzyko wystąpienia majaczenia pooperacyjnego po operacjach onkologicznych, jednak u pacjentów w wieku 75 lat i starszych zmniejszył częstość występowania majaczenia z pobudzeniem (21,4% vs. 71%). Arypiprazol nie wykazał różnic w porównaniu z innymi lekami przeciwpsychotycznymi pod względem skuteczności w łagodzeniu objawów majaczenia, bez rozróżnienia na podtypy, ale jego stosowanie wiązało się z mniejszą liczbą działań niepożądanych. W przypadku majaczenia hipoaktywnego lek ten wykazał zarówno wyższy wskaźnik remisji, jak i poprawę wyniku w skali Memorial Delirium Assessment Scale (MDAS) w porównaniu z haloperydolem. Interwencja z zastosowaniem leków dopaminergicznych wykazała lepszą skuteczność w leczeniu podtypu hipoaktywnego ze współistniejącym nowotworem w stadium terminalnym, podczas gdy wszystkie metody terapeutyczne wykazały podobną skuteczność w porównaniu z placebo w leczeniu i zapobieganiu epizodom majaczenia.

SŁOWA KLUCZOWE

dopamina, majaczenie, arypiprazol, metylofenidat, yokukansan

INTRODUCTION

Delirium is a neuropsychiatric disorder described by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) criteria as a sudden or fluctuating disturbance of consciousness and cognitive function that can be directly caused by another disease unit, intoxication, or withdrawal [1]. The main symptoms relevant to the diagnosis are attention deficits, psychomotor impairment, or circadian cycle alterations. In the clinical picture, delirium can also present as psychosis, fluctuating consciousness, cognitive impoverishment, or affective impairment. However, due to the wide range of factors inducing this entity and the unclear pathogenesis, symptoms are not limited to those listed above [2]. Delirium can be divided into subtypes – hyperactive, hypoactive, and mixed – based on the patient's psychomotor activity, such as agitation, physical activity, or sleep deprivation. The catatonic variant is also distinguished as severe hypoactive delirium and the excited variant as acute hyperactive delirium [3,4,5]. Delirium may affect 10%–24% of all hospitalized patients, 15%–53% of post-operative patients, 60%–80% of critical care patients, and 80%–−90% of terminally ill oncology patients [6,7,8]. Due to the difficult differential diagnosis (depression along with dementia), the hypoactive form of delirium is often diagnosed late, which can lead to poorer prognosis, prolonged hospitalization, and higher mortality [9]. Due to the unclear pathogenesis of delirium, pharmacological treatment is most often based on typical antipsychotic drugs, which act symptomatically to improve the patient's condition, along with analgesics and fluids if needed. In cases of acute agitation and elevated psychomotor drive – as well as withdrawal delirium – central nervous system (CNS) depressants are also used, most often a benzodiazepine, while in delirium of somatogenic etiology, benzodiazepine derivatives should be avoided [10].

The system integration failure hypothesis

A multitude of patient-specific correlations have been described in the development of delirium, while no further unified theory of acute brain failure has been proposed. The current state of knowledge favors the system integration failure hypothesis (SIFH), which is an empirical combination of the neurotransmitter disbalance hypothesis (NTH) and the network dysconnectivity hypothesis (NDH) [11]. The NTH is based on organic alterations of neurotransmitter metabolism, particularly acetylcholine (ACh) and dopamine (DA). Alterations may include the synthesis, degradation, bioavailability, or firing of neurons involved in particular pathways in the CNS. The NDH implies the collapse of the integrated functioning of various neuronal networks, working in cooperation to adequately process receptive information and motor response. The SIFH boils down to identifying correlations between neurochemical and functional changes in the higher centers of the CNS in an attempt to explain the varied phenotypic presentation of delirium. By identifying correlations and shared patterns between alterations in neurotransmitter activity and modifications within complex, interdependent brain networks, this perspective suggests that the earlier theories are better understood as complementary and interrelated rather than mutually exclusive [12,13,14].

Involvement of the ventral tegmental area in the pathogenesis of delirium

Recent neuroimaging reports have revealed the existence of a number of networks responsible for higher CNS function [15]. Many correlations of neuronal communication between CNS centers have been discovered, both in response to interceptive and extraceptive stimuli and in the absence of stimuli. The default-mode network, the executive network, and subcortical connections appear to play crucial roles in the development and clinical picture of delirium. The posterior cingulate cortex (PCC) is considered the node for the disease [16]. The executive network is liable for the centers responsible for attention and working memory (the dorsolateral prefrontal cortex), response selection (the dorsomedial prefrontal cortex/pre--supplementary motor area), and response suppressors (the ventrolateral prefrontal cortex) [17,18,19]. These centers direct attention to appropriate stimuli as behavioral choices are weighed against shifting conditions, homeostatic requirements, and the situational context. The default mode network and the executive network show anticorrelation in intrinsic fluctuations in neuronal activity, which is disrupted during an episode of delirium. Reduced anticorrelation or positive correlation of these interrelated networks can lead to some clinical symptoms, such as reduced awareness of the environment and an inability to respond correctly to the reception of external stimuli [20]. Reduced connections between subcortical regions involving the interlaminar thalamic nuclei, mesencephalic tegmentum, nucleus basalis, and ventral tegmental area (VTA) have also been demonstrated. All of these regions also show impaired interconnection with the striatum area. The intralaminar thalamic nuclei and mesencephalic tegmentum are functionally interconnected and form part of the ascending reticular activating system, which is involved in the regulation of consciousness and arousal [21]. Disturbances of consciousness, crucial in the diagnosis of delirium, suggest the involvement of disturbances of the connection of these regions in the pathophysiology of this disorder. The striatum, which was presumed to play an important role in delirium, also showed reduced interconnections with the rest of the subcortical centers during delirium episodes [22]. One of the causes of the alterations in connections between the subcortical centers mentioned above appears to be impaired dopaminergic transmission. The VTA, which is the site of the bodies of dopaminergic neurons projecting into the mesocorticolimbic pathway, may affect the signal integration of the remaining cortical centers and thus induce acute brain failure, manifested as delirium [23]. Other drugs used in the treatment and prevention of delirium include dexmedetomidine, a selective α-2 adrenergic receptor agonist, producing sedative, anti-anxiety, and sympatholytic effects [24]. Another drug used as a sedative in delirium patients with elevated psychomotor drive is clomethiazole, a vitamin B1 derivative, which is an allosteric modulator of the $GABA_A$ receptor that enhances the action of inhibitory transmitters, primarily GABA (γ-aminobutyric acid) and glycine [25].

The aim of the study was to identify compounds that enhance dopaminergic transmission in somatogenic delirium and to compare their efficacy to classical drugs used in this disease entity. It should be remembered that the pathogenesis of withdrawal delirium is different and the results should not be extrapolated to every type of delirium without knowing its etiology.

MATERIAL AND METHODS

A search of the literature available in MEDLINE (National Library of Medicine, Bethesda, MD) was conducted to identify papers meeting the criteria for this review. The exclusion criteria were (1) language other than English, (2) publication prior to 2005, and (3) any study type other than randomized controlled clinical trials or prospective interventional cohort studies. The inclusion criteria were (1) papers on the pharmacotherapy of delirium, regardless of subtype, (2) administration of dopaminergic substances (DA transporter protein inhibitors, Dx agonists, or Dx partial agonists), (3) delirium from any cause, and (4) consideration of both treatment and prevention. The MEDLINE database was searched using the keywords “delirium” and “pharmaceutical therapy.”

RESULTS

In total, 520 unique articles met the search criteria. The abstracts of 428 were rejected as being irrelevant to the review topic. A manual analysis of the remaining 92 articles revealed 12 articles that met the full criteria (Figure 1). The quantitative data are shown in Table I.

Methylphenidate

Gagnon et al. [26] used methylphenidate (MPH) to improve cognitive function in advanced cancer patients with hypoactive delirium. Using the Mini-Mental State Exam (MMSE), they showed improvement in patients after just one dose of MPH, where the MMSE score increased from a median of 21 (mean: 20.9, SD: 4.9) to 27 (mean: 24.9, SD: 4.7). The maximum score is 30. One patient died before reaching a stable dosage, while the MMSE score of the remaining 13 patients rose to 28 (mean: 27.8, SD: 2.4). All patients showed increased alertness, partial or complete resolution of psychomotor retardation, and normalization of slurred speech. One patient did not improve cognitively, but also showed normalization of psychomotor drive.

Yokukansan

Studies by Sadahiro et al. [27] and Wada et al. [28] showed no difference in the risk of onset of delirium with agitation after invasive oncologic resection.

Patients in the study received either yokukansan (YKS) or a placebo preoperatively 4–8 days before the planned surgery. The Wada et al. [28] study ended with a decision by the Independent Data Monitoring Committee in the interim phase of analysis, where the mean Hospital Anxiety and Depression Scaled Anxiety (HADS-A) score in the study group was 5.0 (n = 37) and the incidence of postoperative delirium was 42% (n = 33). There were no significant differences in HADS-A score between the research and control groups (97.5% CI: 0.4 [0.3, 1.2] vs. 0.5 [0.3, 1.3], p = 0.796). There were also no significant differences in the incidence of postoperative delirium (32% [97.5% CI: 21, 44] vs. 30% [18, 42], p = 0.798). The second study found significant differences in the occurrence of postoperative delirium with agitation in a population of patients 75 years of age or older. Delirium with agitation in this population occurred in 3 of 14 patients (21.4%) in the study group and in 5 of 7 patients (71%) in the control group (OR: 0.11, 95% CI: 0.01–0.87).

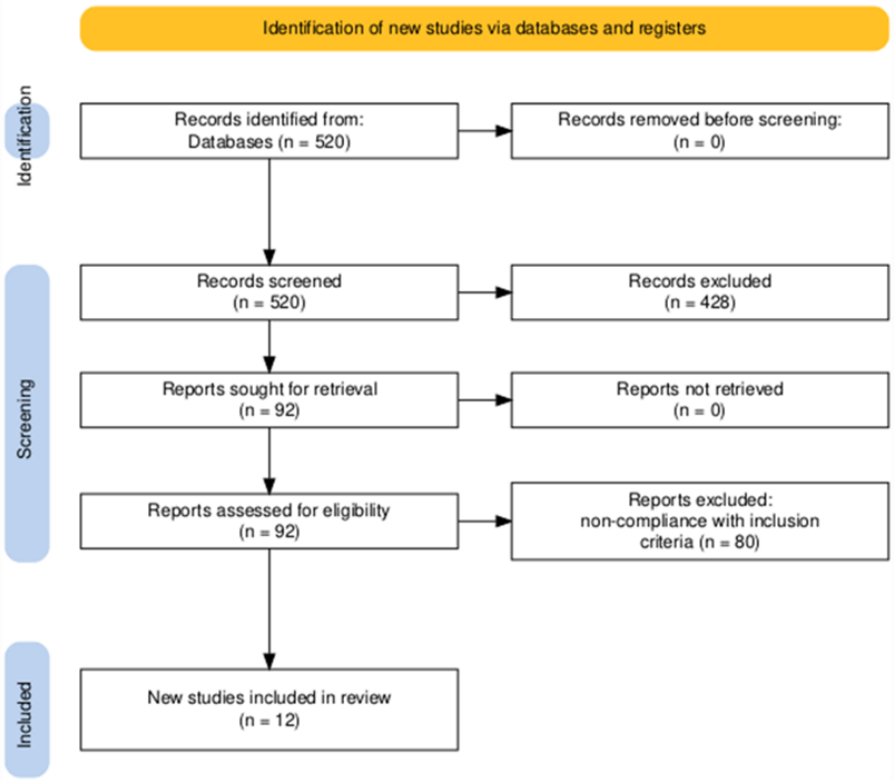

Fig. 1. PRISMA flowchart

Table I. Articles included in this study

Study	Pharmaceutical approach	Main finding
1	2	3
Gagnon et al. [26]	MPH	MMSE score increased to a median of 27 (mean: 24.9; SD 4.7) from 21 (mean: 20.9; SD 4.9) after a single dose.
Sadahiro et al. [27]	YKS	Reduced risk of postoperative delirium with agitation in patients over 75 years of age (OR: 0.11, [95% CI]: 0.01–0.87)
Wada et al. [28]	YKS	No difference in the risk of onset of delirium with agitation after invasive oncologic resection
Boettger and Breitbart [29]	ARI	Higher improvement in MDAS score (15.6 to 5.7 vs. 19.9 to 10.2) and rate of resolution (100% vs. 58.3%) in hypoactive delirium
Mokhtari et al. [30]	ARI	Reduced incidents of delirium in the neurosurgical ICU compared to placebo (55% vs. 20%, p = 0.022)
Nouri et al. [31]	ARI	No difference between ARI and placebo in the prevention of delirium in patients hospitalized in a general ICU
Lee et al. [32]	ARI	No significant differences in efficacy in delirium resolution compared to HAL
Lee et al. [33]	ARI	No significant differences in efficacy in delirium resolution compared to HAL; fewer adverse reactions.
Boettger et al. [34]	ARI	Higher improvement in MDAS score (15.6 to 5.7 vs. 18.8 to 8.1) and rate of resolution (100% vs. 77.8%) in hypoactive delirium compared to HAL

cd. Tab. I

1	2	3
Sugawara et al. [35]	ARI	No difference between ARI and risperidone in treatment efficacy of postoperative delirium. The achieved clinical effect required, on average, a higher chlorpromazine equivalent ARI dose (baseline 270 mg/day vs. 50 mg/day; maximum 330 mg/day vs. 70 mg/day).
Hatta et al. [36]	ARI	ARI was significantly more commonly administered to patients with hypoactive delirium than other antipsychotics (33%, $p < 0.0001$).
Boettger et al. [37]	ARI	A comparison of ARI, HAL, risperidone, and olanzapine showed no differences in the effectiveness of delirium symptom management. ARI and risperidone achieved the most favorable adverse reaction profile.

* MPH – methylphenidate; YKS – yokukansan; ARI – aripiprazole; MMSE – Mini-Mental State Examination; MDAS – Memorial Delirium Assessment Scale; ICU – intensive care unit; HAL – haloperidol.

Aripiprazole

Boettger and Breitbart [29] investigated the efficacy of aripiprazole (ARI) in treating an episode of delirium in hospitalized cancer patients and examined differences in response with respect to the subtype presented. Efficacy was determined by the Memorial Delirium Assessment Scale (MDAS) score at baseline (T1), after 2–3 days (T2), and after 4–7 days (T3). The mean MDAS score during observation declined from 18.0 (T1) to 8.3 (T3). Resolution, defined as a drop in MDAS below a score of 10, was obtained in 52.4% of cases at T2 and 76.2% at T3. A 100% resolution rate was observed in patients with hypoactive delirium compared to 58.3% in patients presenting with hyperactive delirium. A similar trend was observed for improvement in MDAS score (15.6 at T1 to 5.7 at T3 in hypoactive delirium and from 19.9 at T1 to 10.2 at T3 in hyperactive delirium).

Mokhtari et al. [30] found a lower incidence of delirium in the neurosurgical intensive care unit (ICU) setting associated with ARI administration. The control and intervention groups, each with 20 patients, had 11 (55%) and 4 (20%) incidents of delirium onset ($p = 0.022$). The number of delirium-free days was not significantly different (placebo: 4.3, [95% CI]: 3.2–5.4; ARI: 5.6, [95% CI]: 4.6–6.5, $p = 0.111$). No serious adverse reactions were reported.

Nouri et al. [31] found no difference between ARI and placebo in the prevention of delirium in patients hospitalized in a general ICU. The Confusion Assessment Methods for the ICU (CAM-ICUs) was used daily for 7 days as a criterion for delirium diagnosis. No differences were found in the trend of score change in the two groups. Results related to the length of stay in the ICU showed that the use of the ARI shortened the length of hospitalization, whereas the reduction was not statistically significant ($p > 0.05$).

Aripiprazole compared to other antipsychotics

In the literature, ARI is most often compared with the typical antipsychotic drug haloperidol (HAL). The data show no significant differences in efficacy in delirium resolution in studies without distinguishing into subtypes; however, ARI shows a more benign profile of adverse reactions, such as extrapyramidal symptoms (EPS) and hyperprolactinemia [32,33]. In contrast, the study by Boettger et al. [34] was the only one to compare ARI and HAL in overall effectiveness and delirium resolution rates by subtype. Efficacy was measured by the change in MDAS score from T1 (diagnosis of delirium) to T2 (day 7). The study found no difference in delirium resolution without a breakdown into subtypes (76.2% for both HAL and ARI). MDAS scores improved from 18.1 to 8.3 for ARI and from 19.9 to 6.8 for HAL. For patients with hypoactive delirium, MDAS scores improved from 15.6 to 5.7 for ARI and 18.8 to 8.1 for HAL. The resolution of hypoactive delirium was 100% for ARI and 77.8% for HAL. For the hyperactive type, resolution rates were 58.3% for ARI and 75% for HAL. No EPS were recorded for ARI, while there were in 19% of cases for HAL. Among patients receiving HAL, drug-induced parkinsonism occurred in 19% and dystonia in 9%. The incidence of EPS was directly proportional to the dose of HAL and occurred more frequently in the hyperactive phenotype.

Sugawara et al. [35] compared the efficacy of ARI with another atypical antipsychotic, risperidone, in the management of postoperative delirium in patients after cardiovascular surgery. Effectiveness was defined as a reduction in the scores for the Delirium Rating Scale – Revised-98 (DRS-R-98) and the Clinical Global Impression – Severity scale (CGI-S) at baseline and after 7 days of treatment. There were no statistically significant differences in efficacy and a response (defined as a reduction in DRS-R-98 score) was achieved in 60% of cases with ARI and in 80% with risperidone ($p = 0.78$). There was one incident of oversedation in each group, but they fully resolved after the ARI dosage was adjusted and risperidone was discontinued. Otherwise, both drugs were well tolerated by patients. The clinical effect required, on average, a higher chlorpromazine (CP)-equivalent ARI dosage than risperidone at both treatment initiation (CP-equivalent doses of 270 mg/day and 50 mg/day, respectively) and maximum doses (330 mg/day and 70 mg/day).

A prospective observational study conducted by Hatta et al. [36] included 2,353 patients who were being treated with antipsychotics for delirium and admitted to general hospitals. ARI was significantly more commonly administered to patients with hypoactive delirium than other antipsychotics (33%, $p < 0.0001$).

Twenty-two serious adverse events (0.9%) were recorded, including aspiration pneumonia (17 patients), cardiovascular events (4 patients), and venous thromboembolism (1 patient). None of the above occurred in the ARI group. EPS were the only adverse effects in this group, with a prevalence of 3.3% (the lowest of all, although not statistically significant).

A comparison of ARI, HAL, risperidone, and olanzapine showed no differences in the effectiveness of managing delirium symptoms as measured by improvement in MDAS score between these drugs. No differences in delirium resolution rates were observed either. In the ARI group, 9.5% of patients showed a worsening of delirium and required modification of treatment; no other adverse reactions were reported. Treatment with HAL significantly increased the rate of EPS (19%), whereas olanzapine-managed patients showed the most excessive sedation (28.6%). ARI and risperidone achieved the most favorable adverse reaction profile [37].

DISCUSSION

Methylphenidate

A study by Gagnon et al. [26] showed improved cognitive function and re-regulation of psychomotor drive in terminal cancer patients with co-existing hypoactive delirium. MPH is a benzopiperidine derivative, occurring as four stereoisomers, and it thus has two stereogenic centers [38]. One pair of erythoisomers and one of threoisomers can be distinguished, of which d-threo-methylphenidate shows the most expected clinical properties [39]. MPH is a psychostimulant and increases the activity of the CNS. The therapeutic effect has been ascribed to its neurostimulation of the reticular activation system. The main molecular mechanism of action is based on inhibition of dopamine (DAT) and, to a lesser extent, norepinephrine transport (NET) proteins. Thus, MPH is a dopamine and norepinephrine reuptake inhibitor [40]. In addition, MPH binds to serotonin transport (SERT) protein and serotonin receptors (5-HT_{A1} and 5-HT_{B2}), with interactions distinguished by significantly higher IC_{50} values and a lack of clinical relevance (for dl-MPH: IC_{50} (DAT) = 20 mM; IC_{50} (NET) = 51 mM; IC_{50} (5-HT_{A1}) = 10,000 mM) [41,42]. Furthermore, MPH selectively redistributes the vesicular monoamine transporter 2 (VMAT-2), altering pools of vesicles by reducing the quantity of vesicles to be recycled. Unlike amphetamine, which works by a similar mechanism, MPH induces the redistribution of vesicles from the plasmalemmal-membrane-associated fraction to the cytoplasmic, non-membrane-associated fraction. This reduces the risk of neurotoxicity and the accumulation of neurotransmitters in the cytoplasm of perikaryon endings, which promotes the formation of reactive oxygen species [43,44,45]. VMAT-2 redistribution alters dopaminergic transmission in neurons in a different mechanism than conventional DAT inhibition.

The heuristic model of dopaminergic transmission is based on tonic-phasic interaction [46]. Extrasynaptic stores modulate tonic activity, which in turn is the main regulatory mechanism of phasic activity. Through the mechanism of VMAT-2 redistribution and increasing the pool of synaptic vesicles available for exocytosis from nerve endings, MPH mimics the tonic activity of dopaminergic transmission [47]. The dysfunctions exhibited by patients with hypoactive delirium – predominantly short-term memory and apraxia dysfunction – may be related to dysregulation of tonic-phasic dopaminergic mesolimbic pathway activity, originating in the VTA. In addition, the hippocampal subiculum appears to modulate the mesolimbic pathway, not only directly but also indirectly, so that MPH may increase phasic DA spikes of hippocampal centers to regulate the mesolimbic pathway in a modulator activation mechanism [48]. The dysfunction can be extended to disequilibrium-induced tonic-phasic activity of the mesolimbic pathway, which is clinically expressed in hypoactive delirium. Therefore, MPH, by increasing extrasynaptic DA concentration through a reuptake blockade and VMAT-2 redistribution, may regulate the tonic-phasic activity of the mesolimbic pathway [49]. This may have a restoration effect on the interaction balance of the limbic system centers, the action of which affects the activity of centers in both the limbic system and the rest of the subcortical nuclei, whose impaired connection has been shown during an episode of delirium.

Yokukansan

YKS is an herbal drug used in traditional Japanese medicine to treat insomnia, nighttime crying in children, and neurosis [50]. YKS consists of seven medicinal herbs, including *Atractylodes lancea* rhizome (4.0 g, rhizome of *Atractylodes lancea* De Candolle, *Compositae*), poria sclerotium (4.0 g, sclerotium of *Poria cocos* Wolf, *Polyporaceae*), cnidium rhizome (3.0 g, rhizome of *Cnidium officinale* Makino, *Umbelliferae*), uncaria thorn (3.0 g, hook of *Uncaria rhynchophylla* Miquel, *Rubiaceae*), Japanese Angelica root (3.0 g, root of *Angelica acutiloba* Kitagawa, *Umbelliferae*), bupleurum root (2.0 g, root of *Bupleurum falcatum* Linne, *Umbelliferae*), and glycyrrhiza root (1.5 g, root and stolon of *Glycyrrhiza uralensis* Fisher, *Leguminosae*). Its methanol fraction of liquid chromatography contains more than 25 active substances, which are summarized in Table II.

Studies have shown that YKS can be clinically effective in reducing behavioral and psychological symptoms of dementia (BPSD) and improving psychotic manifestations such as delusions or hallucinations associated with dementia as well as overlapping delirium. Furthermore, YKS improved scores on the Neuropsychiatric Inventory (NPI) subscale of agitation in patients with dementia [52].

Table II. Main active compounds in yokukansan (based on [51])

Crude drug name	Composition (g)	Major compounds
Atractylodes lancea	4.0	Atractylodin, eudesmol
Poria cocos	4.0	Eburicoic acid, ergosterol
Cnidium officinale	3.0	Cnidilide, butylphthalide
Uncaria rhynchophylla	3.0	Rhynchophylline, geissoschizine methyl ether
Angelica acutiloba	3.0	Ligustilide, falcarinol
Bupleurum falcatum	2.0	Saikosaponin A, C, D, E
Glycyrrhiza uralensis	1.5	Glycyrrhizin, liquiritin

The presumed mechanism of action of YKS is based on modulation of serotonin receptors (5-HT_{1A}, 5-HT_{2A}, and 5-HT_3) and dopamine D_1 receptors in the prefrontal cortex (PFC) and inhibition of catechol-O-methyl-transferase (COMT) activity [53,54,55]. A study by Ueki et al. [56] showed a greater density of 5-HT_{1A} receptors in the PFC in socially isolated YKS--supplemented mice, which was thought to mediate augmentation of the behavioral response to the 5-HT_{1A} receptor agonist (±)-8-hydroxy-2-(dipropylamino) tetralin hydrobromide (8-OH-DPAT). The active substance responsible for the partial agonist activity of YKS against 5-HT_{1A} receptors is geissoschizine methyl ether (GM), an indole alkaloid isolated from uncaria hook [57]. Additionally, it has been shown that YKS downregulates the expression of 5-HT_{2A} receptors in the PFC, which has been suggested as a synergistic action of bupleurum root, uncaria hook, Japanese angelica root, and glycyrrhiza root. Furthermore, YKS reduces the hallucination-like behavior (head-twitching) induced by 5-HT_{2A} receptor agonist 2,5--dimethoxy-4-iodoamphetamine (DOI) in both normal mice and stressed mice [58]. Moreover, the alkaloids in YKS exhibit antagonistic activity against 5-HT_{3A} and 5-HT_{3AB} receptors (IC_{50} = 5.27 µM and IC_{50} = = 5.14 µM, respectively) [54]. In addition, age-related deficits of working memory and reversal learning, associated with a decrease in dopaminergic transmission in the prelimbic region of the PFC, were reversed by administering YKS to rats for a period of 3 months [59,60]. The ameliorating effects of working memory deficits and reversal learning were revoked by infusions of the D_1 receptor antagonist SCH23390 [53]. Thus, a possible mechanism for ameliorating age--related cognitive deficits associated with a decrease in extracellular dopamine levels in prefrontal cortical regions is modulation of the D_1 receptor by YKS [61]. It has been shown that some alkaloids contained in YKS (GM and corynoxeine, from uncaria hook), as well as YKS itself, inhibit COMT activity in a similar manner to the COMT inhibitor entacapone. The investigated effects of YKS on DA synthesis from L-3,4-dihydroxypheny-lalanine (L-DOPA) in the 5-HT synthetic cell line RIN 14B showed augmented DA production along with inhibition of its metabolism to 3-methoxytyramine (3-MT) [55].

Activation of 5-HT_{1A} receptors in the medial PFC (mPFC) of mice at lower dosages by the selective agonist BAYx3702 (3 µM) caused an increase in firing rate and bursting fire of dopaminergic neurons in the VTA and DA release in the VTA and mPFC, while higher dosages (30 µM) led to a reduction [62]. Both of these effects disappeared in 5-HT_{1A} knock-out mice, suggesting a direct correlation. YKS alkaloids exhibiting partial agonist activity toward mPFC 5-HT_{1A} receptors may potentiate VTA DA neuronal activity and mesocortical DA release. Both systemic and direct administration of DOI to the PFC increased firing rate and DA release in the VTA, which was reversed by the selective 5-HT_{2A} receptor antagonist M100907 [63]. Although activation of the 5-HT_{2A} receptor affects DA release in the mesocortical pathway, 5-HT_{2A} antagonists have no effect on basal dopamine release in the PFC, VTA, or nucleus accumbens (NAcc), suggesting the involvement of the 5-HT_{2A} receptor on phasic but not tonic DA release [64,65]. The down-regulation of 5-HT_{2A} expression and reduction of DOI (5-HT_{2A} agonist) effects by YKS suggests an ameliorating effect on aggressive, hallucination-like, and anxiety-like behaviors, without directly affecting tonic DA secretion in the mesocortical pathway [66]. On the other hand, dopaminergic neuronal activity is inhibited by the antagonistic action of YKS alkaloids on 5-HT_3 receptors. Preclinical studies indicate that 5-HT_3 receptor antagonism in the VTA, NAcc, and amygdala reduces alcohol self-administration in rats and minimizes alcohol-associated effects that are attributable to phasic DA firing within the VTA [67]. Therefore, 5-HT_3 antagonism may inhibit dopaminergic neuronal activity in the VTA and reduce DA levels throughout the mesocorticolimbic pathway.

The broad receptor profile of the active ingredients contained in YKS and the interactions of serotonergic and dopaminergic systems determine the extensive pharmacodynamics of this traditional Japanese medicine [50]. Clinical data showed no effect of premedication with YKS prior to surgical resection in the general population on either the risk of a postoperative delirium episode or HADS-A test score. However, when the patients' ages were taken into account, YKS reduced the number of delirium incidents with agitation in people older than 75 years.

Dopaminergic neurons are exposed to high levels of reactive oxygen species, which are formed in DA metabolism. Physiological protective mechanisms against increased oxidative stress include the endogenous antioxidant defense system (EADS) and repair mechanisms of neuronal divergence within CNS structures. Vigilance of EADS decreases with age, which increases the sensitivity of dopaminergic neurons to oxidative stress. Repair mechanisms also weaken with age as the expression of aggrecan, a major component of local extracellular matrix thickenings, increases. The perineuronal nets formed by these thickenings impede neuronal differentiation [68,69]. This results in a linear fallout of dopaminergic neurons with a prevalence of 5%–10% per decade [70]. Disturbed dopaminergic neurotransmission, which may be a risk factor in the etiopathology of delirium, therefore increases with age, perhaps explaining the results obtained by Sadahiro et al. [27] YKS, through its multivector direct and indirect action on the dopaminergic system, may increase the activity of the PFC and the VTA, involved in the mesocortical pathway, which presumably was a protective factor for the onset of a postoperative delirium with agitation episode in patients aged 75 and older.

Aripiprazole

ARI, an atypical neuroleptic, has a unique pharmacological profile with potent partial agonist activity at the D_2 and 5-HT_{1A} receptors [71,72]. In addition, it exhibits modest antagonist affinity for 5-HT_2 and 5-HT_7 receptors, α_1-adrenoreceptors, and H_1 histaminergic receptors [73]. It shows high affinity for presynaptic dopamine autoreceptors, located on dopaminergic neurons of the VTA and substantia nigra, which are involved in DA synthesis and release [74]. These receptors, acting through a brake-type mechanism, inhibit DA release in response to increased firing of dopaminergic neurons [75]. A series of clinical studies showed ARI's bidirectional action on dopaminergic neurotransmission, demonstrating agonist activity in hypodopaminergic conditions and antagonist activity in hyperdopaminergic conditions [76]. As mentioned above, partial agonist activity at the 5-HT_{1A} receptor results in dose-dependent effects on DA secretion in dopaminergic VTA neurons and modulation of firing rate and bursting fire of such neurons. Clinically, 5-HT_{1A} activation is associated with the antidepressant and anxiolytic actions of ARI [77]. Compared to typical neuroleptics, ARI shows a lower risk of adverse actions [37,78]. This could be related to its narrow receptor profile and partial agonist affinity for the D_2 receptor. The former involves a negligible antagonist affinity for the M_1 receptor, which reduces the risk of both central and peripheral anticholinergic actions. Cholinolytic action has been associated with a higher risk of onset of a delirium episode, which may imply the inappropriateness of using typical neuroleptics (which exhibit strong anticholinergic action) to treat psychotic manifestations in the course of delirium [79]. Furthermore, ARI activity on presynaptic dopamine autoreceptors may reduce the risk of excessive blockade of dopaminergic neurotransmission presenting as EPS effects [80].

The studies referenced above suggest no difference in the efficacy of ARI compared to other antipsychotics; furthermore, some of the studies indicate an advantage for ARI in both delirium symptom management and overall delirium rate of resolution in the hypoactive subtype. The low risk of pharmacokinetic interactions supports the idea of using ARI in hypoactive delirium, which is most commonly seen in palliative patients frequently receiving chemotherapy or opioids. ARI shows a more benign adverse reaction profile, such as EPS or sedation, compared to other antipsychotics, which may favor the choice of ARI in vulnerable groups. Excessive sedation in elderly patients with delirium may lead to a higher risk of dizziness, vertigo, and falls, which – in this age group, due to the prevalence of bone mass loss – may increase the risk of low-energy fractures.

Decreased psychomotor activity associated with the hypoactive phenotypic presentation of delirium may be related to executive network alterations. The centers involved in the processes of receiving intraceptive as well as extraceptive stimuli, their processing, and the selection of behavioral and motor responses are closely linked to dopaminergic transmission. The executive network and the default mode network exhibit an anticorrelation under physiological conditions, with the former processing behavioral reactions in response to an extraceptive stimulus and the latter in response to an intraceptive stimulus or the absence of stimuli. The observed reduction in anticorrelation or positive correlation results in a clinical picture more similar to the phenotype of hypoactive delirium. In addition, alterations in the interconnection of subcortical centers, which are also dependent on dopaminergic neurotransmission, may be involved in the disturbance of consciousness in the course of delirium. However, these are present in both subtypes and are a prerequisite for diagnosing this disease entity. In conclusion, ARI's higher efficacy in both resolution rate and improving MDAS score in patients with hypoactive delirium may be related to its agonist activity against the D2 receptor in a state of hypodopaminergia in centers involved in behavioral response and regulating consciousness.

CONCLUSIONS

The proposed pathogenesis based on alterations in dopaminergic neurotransmission in brain regions involved in executive mechanisms of higher CNS and subcortical consciousness-regulating centers may explain the clinical picture of delirium patients, especially in the hypoactive phenotype. The clinical studies presented here support the possibility of using a therapeutic approach based on dopaminergic substances in both the basic treatment regimen for patients with hypoactive delirium and adjuvant therapy in the

course of deteriorating cognitive function. In addition, preoperative administration of YKS in people older than 75 years may be a protective factor against the onset of postoperative delirium with agitation. The low risk of adverse actions supports this idea, since it applies to older people, often with multiple diseases. In addition, preventive interventions have not shown a statistically significant reduction in the risk of delirium in the general population. The limiting factor of the selected studies was the small sample size, which affects the reliability of the results, and the fact that both prevention and pharmacotherapy of delirium were considered, meaning that no general conclusions can be drawn. Larger, well-controlled clinical studies are needed to determine whether the use of substances that enhance dopaminergic neurotransmission can promote the therapeutic process of patients with the hypoactive delirium subtype.

Conflict of interest

The authors declare no conflict of interest.

Funding

Not applicable

Institutional Review Board Statement

Not applicable

Authors' contribution

Study design – N. Świderski, A. Bielecka-Wajdman
Data collection – N. Świderski
Manuscript preparation – N. Świderski
Literature research – N. Świderski
Final approval of the version to be published – N. Świderski, A. Bielecka-Wajdman

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