

The challenge of managing severe delirium: an observational study of the effects of pharmacological and supportive care on delirium duration and resolution in 602 patients

Carl Moritz Zipser (✉ carlmoritz.zipser@balgrist.ch)

Balgrist University Hospital <https://orcid.org/0000-0002-4396-4796>

Peter Hayoz

UniversitätsSpital Zurich Klinik für Nuklearmedizin

Silvana Knöpfel

UniversitätsSpital Zurich

Peter Peyk

UniversitätsSpital Zurich

Maria Schubert

Zürcher Hochschule für Angewandte Wissenschaften

Roland von Känel

UniversitätsSpital Zurich

Soenke Boettger

UniversitätsSpital Zurich

Research article

Keywords: Delirium, antipsychotics, psychotropics, polypharmacy, confusion

Posted Date: December 13th, 2019

DOI: <https://doi.org/10.21203/rs.2.18810/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background: Delirium is the most common neuropsychiatric disorder seen in hospitalised patients. Current guidelines recommend only using antipsychotics with distressed patients. Nonetheless, in routine clinical practice, multiple psychotropics are commonly administered. More evidence on the short-term benefits of various management approaches in patients with delirium is required.

Methods: In this observational cohort study, 602 delirious patients were followed for twenty days. Supportive care was provided to all patients in addition to either no psychotropic therapy, monotherapy, dual therapy, or polytherapy defined as three or more psychotropic drugs. The effectiveness of interventions regarding delirium resolution and symptom severity was determined by Cox proportional hazards regression and generalized estimating equation models.

Results: Psychotropics were commonly used to manage delirium. In total, 12.1% of patients received polytherapy, 37.2% dual therapy, 37.7% monotherapy, and 12.1% supportive care alone (i.e., almost half of the patients received \geq two psychotropics). Patients who received polytherapy had higher initial baseline delirium severity and exposed the mixed subtype more often; with the latter delirium lasted longer and recovery was less frequent than in mild delirium. Providing supportive care alone in mild delirium was superior to all psychotropic approaches.

Conclusions: In routine clinical practice, the use of multiple psychotropics is common. In our study, however, despite combined supportive management and polypharmacy, patients with severe delirium suffer longer from delirium and have lower resolution rates. For the management of patients with mild delirium supportive care alone can be considered. When psychotropics are considered, single psychotropics and dose optimisation are recommended. These findings underline the challenge of managing severe delirium.

Background

Delirium is a neuropsychiatric disorder characterised by the sudden onset and fluctuating course of disturbed consciousness and cognition, caused by one or often multiple aetiologies. Further features of delirium are sleep-wake cycle disturbances and psychomotor alterations which define the subtypes of delirium [1].

Delirium is the most prevalent neuropsychiatric complication across healthcare settings. On in-patient Medicine wards, its prevalence ranges from 18 to 35% [2], and it is also common in neurology and neurosurgery [3, 4]. Among surgery patients post-operatively, its prevalence depends upon the type of surgery, ranging up to more than 50% after cardiac surgery [5]. Moreover, these estimates might be lower than true rates, as delirium is generally under-recognised and under-managed [6], despite its potential short- and long-term consequences for patients. These include prolonged hospitalisation [7], accelerated cognitive decline, progression to dementia, and increased mortality [8, 9], among others.

Several predisposing risk factors for delirium have been identified. Widely-accepted ones are advanced age, pre-existing dementia, more severe illness, and alcohol use [10]. Often, precipitating factors co-exist, which include infections, systemic inflammation, traumatic brain injuries, and various potentially mind-altering medications (e.g., corticosteroids, opiates, benzodiazepines, antibiotics) [11]. The aetiopathogenesis and underlying neuro-humoral interactions of delirium are complex, including neurotransmitter dysregulation and neuronal network alterations; but, ultimately, they merge into a common pathway of system integration failure [2].

The management of delirium consists of both non-pharmacological and pharmacological strategies to prevent or, once evident, ameliorate the symptoms of delirium. The first priority in delirium management is to eliminate underlying aetiologies. Non-pharmacological strategies include providing sufficient pain management and adequate fluid intake, striving to preserve or restore normal circadian rhythms, ensuring a calm environment and familiar caregivers, and enacting early patient activation and mobilisation. Pharmacological strategies include psychotropic drugs

Administration of haloperidol has long been considered the primary option to treat symptoms of delirium [12]. Current clinical guidelines from the National Institute for Health and Care Excellence (NICE) recommend short-term haloperidol or olanzapine. Alternatively, the cautious use of antipsychotic drugs is recommended in patients with severe distress and those patients at risk to harm themselves or their surroundings after non-pharmacological interventions were not effective or not applicable [13]. This approach is supported by the results of recent randomized controlled trials [14, 15]. Despite this evidence, the administration of multiple psychotropics remains common practice [16].

To date, the effects of concomitant or sequential use of multiple psychotropics to manage delirium are unknown. Therefore, the aim of the current study was to evaluate the benefits of various delirium management approaches in routine clinical practice. We hypothesised that patients show no clinically relevant benefit from multiple-drug regimens. We also compared the use of psychotropics versus supportive care alone.

Methods

Patients

All patients in this study were prospectively enrolled at the University Hospital of Zurich, Switzerland, a tertiary care centre, from regular units across all departments between July 2012 and June 2015. The results are presented in accordance with the STROBE statement [17].

Inclusion criteria were being a consenting adult, having an episode of delirium, and having Delirium Observation Screening scale scores, DOS, over 72 hours or longer [1, 18]. Exclusion criteria were age 18 or younger, short-term hospitalisation (< 24 hours), and missing DOS scores.

The study was approved by the Canton of Zurich Ethics Committee (PB2016-01264).

Procedures

All enrolled patients were assessed three times per day with the Delirium Observation Screening scale over a period of twenty days or until discharge from the hospital. Each of the 13 DOS items, reflecting DSM-IV criteria (American Psychiatric Association, 1994), is rated as either 0 (never) or 1 (occasional to always). For our purposes, delirium was defined as either a single score of three and more, or a 24-hour summation score of seven and more. Upon suspicion of incident delirium, the short version of the Confusion Assessment Method (CAM), with its four items reflecting DSM-III-R criteria (American Psychiatric Association, 1987), was used to confirm the diagnosis. Subtyping of delirium was based on the patient's psychomotor presentation, into hypoactive, hyperactive or mixed subtype, as reflected by DOS items 10, 11 and 13 [19]. Delirium resolution was defined as a DOS-score < 3 points in three assessments over 24-hours.

All patients were managed according to an algorithm already established at the University Hospital Zurich (Appendix 1). Non-pharmacological care basically followed the long-standing concept of reality orientation for patients with cognitive disorders [20]. Additionally, supportive means (e.g. adequate pain management, light-management for the restoration of sleep-wake cycle) were provided by constant caregivers.

Statistical methods

Analyses were performed using the Statistical Package for the Social Sciences, version 25 (SPSS, v. 25) and R version 3.5.3 and the "survival" package (R Foundation for Statistical Computing, Vienna, Austria).

Baseline characteristics were described depending on their parametric properties, either as medians and inter-quartile ranges, or as means and standard deviations. Subjects were categorised into the four pre-defined management approaches: (1) non-pharmacological therapy/supportive care alone; (2) one psychotropic drug (monotherapy); (3) two psychotropic drugs (dual therapy); or (4) three or more psychotropic drugs (polytherapy). Only psychotropics deemed relevant to delirium management were included. Those deemed irrelevant – like antidepressants, mood stabilizers and stimulants – were excluded.

Psychotropic medications were categorised into either: (a) antipsychotics, including haloperidol, pipamperone, risperidone, olanzapine, and quetiapine; or (b) benzodiazepines, including lorazepam and midazolam. Mean daily dosages were determined by dividing the cumulative dose administered by the total number of days administered. Doses considered clinically relevant were: ≥ 1 mg haloperidol; ≥ 20 mg pipamperone; ≥ 1 mg risperidone; ≥ 2.5 mg olanzapine; ≥ 25 mg quetiapine; ≥ 1 mg lorazepam; and ≥ 7.5 mg midazolam. Medications dosed below these ranges were deemed irrelevant and omitted from further analysis.

All continuous variables were tested for normality with the Shapiro-Wilk test. Non-parametric testing for non-normally distributed variables was done with the Mann-Whitney U test for baseline severity of

delirium, delirium subtype, drug dosages and gender comparison between management approaches. The Kruskal-Wallis H test was applied to compare groups on age. For categorical variables simple logistic regression analysis was used. For psychiatric comorbidities and delirium subtypes Pearson- χ^2 analysis was performed. Odds ratios (OR) were calculated for patient groups with different management approaches. When the number of subjects in a given group was less than 20, i.e. in the analysis of risperidone, olanzapine and quetiapine administration, Fisher's exact test was used where appropriate. A one-way ANOVA with post-hoc Bonferroni adjustment with a CI of 95% was carried out for investigating differences in psychiatry transfer and mortality.

To compare the effectiveness between different management approaches, a Cox proportional hazards model was calculated with baseline delirium severity set as a covariate and 'supportive care alone' set as the reference state. A graphic representation displays 'day of observation' as the time variable (x axis) and 'delirium resolution' as the status variable (y axis). Proportional hazards (PH-) assumption was tested with Schoenfeld residuals. Schoenfeld residuals approve the PH-assumption for management groups ($\rho = -0.0795$, $P = 0.088$) in the presence of baseline delirium severity (DOS-score day 1) as a covariate.

With respect to the data distribution, i.e. higher baseline severity in polytherapy compared to supportive care only and monotherapy, to further investigate the relation between delirium severity and management, a generalized-estimating-equations (GEE) model was implemented with gamma-distribution and log-link. A within-subject effect delirium score per day was set, and baseline DOS-score introduced as split-half group factor. This means, that DOS-scores of all patients were dichotomized, for this analysis, according to their baseline delirium severity, and categorized into the higher- or lower- severity group (split-half). Model effects were tested with χ^2 analysis. The day of delirium resolution was tested with regards to baseline severity irrespective of the management group (DOS-score day 1 * Days of observation) and for the management groups (DOS-score day 1 * Days of observation * Management groups). For missing values, the 'last observation carried forward' method was applied. For all inferential testing, statistical significance was defined as $P < 0.05$.

Results

Sociodemographic and clinical characteristics

A total of 602 delirious patients were identified who met inclusion criteria and were sub-categorized into the four management approaches: supportive care alone ($n = 78$; 13.0%); monotherapy ($n = 227$; 37.7%); dual therapy ($n = 224$; 37.2%); polytherapy ($n = 73$; 12.1%). Mean ages for the four treatment groups were similar, ranging from 69.4 to 72.1 years ($P = 0.24$). In all groups, subjects were predominantly male, the percentage ranging between 57 and 70%. The only statistically significant between-group difference in gender distribution was comparing those on dual therapy (70%) versus monotherapy or supportive care alone (each 57%, $P = 0.033$ and $P = 0.006$, respectively). Sociodemographic and delirium characteristics are summarised in Table 1.

Table 1

Demographics, baseline clinical characteristics and outcome measures, *mean (standard deviation (SD), range), **Days to resolution of delirium was estimated in split-half groups and not in whole groups, due to distribution of delirium severity.

	Group 2	Group 3	Group 4	
	Monotherapy	Dual therapy	Polytherapy (≥ 3)	Statistically-significant differences between groups
N =	227 (37.7%)	224 (37.2%)	73 (12.1%)	
% of patients given lorazepam	24.7%	51.3%	69.9%	Group 4 > Group 3 > Group 2
Median dose (IQR)	2 (4)	4.5 (8)	6 (11.5)	Group 4, 3 > Group 2
% of patients started on drug on day #1	14.1%	30.4%	43.8%	Group 4 > Group 3 > Group 2
% of patients given midazolam	13.2%	24.6%	43.8%	Group 4 > Group 3 > Group 2
Median dose (IQR)	29.5 (46)	15 (125)	35 (154)	None
% of patients started on drug on day #1	3.5%	9.9%	7.3%	Group 3 > Group 2
% of patients given haloperidol	21.1%	49.6%	82.2%	Group 4 > Group 3 > Group 2
Median dose (IQR)	2 (7)	6 (14)	9.25 (12)	Group 4, 3 > Group 2
% of patients started on drug on day #1	13.7%	33.5%	47.9%	Group 4 > Group 3 > Group 2
% of patients given pipamperone	48.0%	75.9%	91.8%	Group 4 > Group 3 > Group 2
Median dose (IQR)	220 (280)	245 (315)	420 (530)	Group 4, 3 > Group 2
% of patients started on drug on day #1	41.0%	54.5%	68.5%	Group 4 > Group 3 > Group 2
% of patients given risperidone	4.8%	8.0%	13.7%	Group 4 > Group 2
Median dose (IQR)	7.5 (9.5)	9 (11)	12 (15)	None
% of patients started on drug on day #1	3.2%	3.7%	4.3%	None

	Group 2	Group 3	Group 4	
% of patients given olanzapine	2.2%	2.2%	9.6%	None
Median dose (IQR)	30 (35)	42.5 (105)	15 (27.5)	None
% of patients started on drug on day #1	2.7%	1.8%	4.3%	None
% of patients given quetiapine	13.2%	15.6%	15.1%	None
Median dose (IQR)	337.5 (906)	300 (525)	125 (350)	None
% of patients started on drug on day #1	8.8%	12.0%	6.8%	None

In terms of reasons for admission, neurological and medical disorders were most common, accounting for almost three-quarters of admissions, followed by oncological diseases (15%) and trauma (7%). Psychiatric disorders were present in one fifth of patients: dementia in 7%, an affective disorder in 5%, a substance use disorder in 5%, and psychosis in 2.5%. All psychiatric comorbidities occurred equally across the four management groups ($P = 0.43$).

Prior to admission, 8.6% of patients had received at least one antidepressant (serotonin-reuptake inhibitor, tricyclic antidepressant or atypical antipsychotic).

Transfers to inpatient psychiatry and mortality in non-pharmacological management versus monotherapy, dual therapy and polytherapy were without statistically significant differences (Table 1). Patients with high baseline delirium severity were prone to receive more medications. Furthermore, fewer patients with high baseline delirium severity were diagnosed with hypoactive subtype (Table 1). Within the first day of management, patients on polytherapy were more delirious (mean DOS score 17.7) than those managed with support only (12.1; $P = 0.002$), and those on single psychotropics (14.4; $P = 0.027$). Comparing those on poly- and dual therapy, baseline delirium severity was the same ($P = 0.24$). In patients on dual therapy, delirium was more severe than among those receiving supportive care alone ($P < 0.001$) or monotherapy ($P = 0.01$). Furthermore, patients on monotherapy were more delirious than those receiving supportive care alone ($P = 0.003$).

There were some differences in the prevalence of delirium subtypes between management approaches: the mixed subtype was more common in patients on two or more medications versus either monotherapy ($P = 0.02$) or supportive care alone ($P = 0.007$). In those patients on dual- versus poly-therapy no differences were noted in the prevalence of the mixed subtype ($P = 0.35$). There were no group differences in the prevalence of hyper- and hypoactive subtypes.

Pharmacological management of delirium: general characteristics

In total, 49.3% of patients received at least two psychotropic drugs, whereas 50.7% received one or none. Three out of four patients (78.1%) on polytherapy received two or more psychotropic medications on the first day of management; and, irrespective of the number of psychotropics administered, nearly half of our patients received one benzodiazepine.

Among patients with pharmacological therapy (N = 524) 66.0% received pipamperone, 42.4% received lorazepam, 41.8% received haloperidol, 25.2% received midazolam, 14.5% received quetiapine, 7.4% received risperidone and 3.2% received olanzapine.

Table 2 summarises the administration of psychotropics across all forms of pharmacotherapy management.

	<u>Group 2</u>	<u>Group 3</u>	<u>Group 4</u>	
	Monotherapy	Dual therapy	Polytherapy (≥ 3)	Statistically-significant differences between groups
N =	227 (37.7%)	224 (37.2%)	73 (12.1%)	
% of patients given lorazepam	24.7%	51.3%	69.9%	Group 4 > Group 3 > Group 2
Median dose (IQR)	2 (4)	4.5 (8)	6 (11.5)	Group 4, 3 > Group 2
% of patients started on drug on day #1	14.1%	30.4%	43.8%	Group 4 > Group 3 > Group 2
% of patients given midazolam	13.2%	24.6%	43.8%	Group 4 > Group 3 > Group 2
Median dose (IQR)	29.5 (46)	15 (125)	35 (154)	None
% of patients started on drug on day #1	3.5%	9.9%	7.3%	Group 3 > Group 2
% of patients given haloperidol	21.1%	49.6%	82.2%	Group 4 > Group 3 > Group 2
Median dose (IQR)	2 (7)	6 (14)	9.25 (12)	Group 4, 3 > Group 2
% of patients started on drug on day #1	13.7%	33.5%	47.9%	Group 4 > Group 3 > Group 2
% of patients given pipamperone	48.0%	75.9%	91.8%	Group 4 > Group 3 > Group 2
Median dose (IQR)	220 (280)	245 (315)	420 (530)	Group 4, 3 > Group 2
% of patients started on drug on day #1	41.0%	54.5%	68.5%	Group 4 > Group 3 > Group 2
% of patients given risperidone	4.8%	8.0%	13.7%	Group 4 > Group 2
Median dose (IQR)	7.5 (9.5)	9 (11)	12 (15)	None
% of patients started on drug on day #1	3.2%	3.7%	4.3%	None
% of patients given olanzapine	2.2%	2.2%	9.6%	None
Median dose (IQR)	30 (35)	42.5 (105)	15 (27.5)	None
% of patients started on	2.7%	1.8%	4.3%	None

drug on day #1				
% of patients given quetiapine	13.2%	15.6%	15.1%	None
Median dose (IQR)	337.5 (906)	300 (525)	125 (350)	None
% of patients started on drug on day #1	8.8%	12.0%	6.8%	None

Table 2

Psychotropic drugs given. IQR: interquartile range.

Administration of psychotropics: antipsychotics and benzodiazepines

The psychotropics most commonly used in monotherapy were pipamperone (48.0%), followed by lorazepam (24.7%) and haloperidol (21.1%).

The number of several specific medications administered increased from mono- to dual- to polytherapy. Patients on polytherapy more often received haloperidol (OR = 17.2, CI 8.7–33.9, $P < 0.001$), olanzapine (OR = 4.7, CI 1.4–15.3, $P = 0.011$), risperidone (OR = 3.1, CI 1.3–7.7, $P = 0.016$), pipamperone (OR = 12.1, CI 5–29; $P < 0.001$), and one of the benzodiazepines (OR = 17.2, CI 5.8–19.5; $P < 0.001$) than those on monotherapy. Patients on poly- versus dual-therapy more commonly received haloperidol (OR = 4.7, CI 2.4–9, $P < 0.001$), olanzapine (OR = 4.6, CI 1.4–15.1, $p = 0.011$), pipamperone (OR = 3.5, CI 1.5–8.6; $P = 0.002$), and a benzodiazepine (OR = 3.7, CI 2.1–6.5; $P < 0.001$). Patients on dual versus monotherapy more often received haloperidol (OR = 3.7, CI 2.4–5.5, $P < 0.001$), pipamperone (OR = 3.4, CI 2.3–5.1, $P < 0.001$) and a benzodiazepine (OR = 2.8, CI 1.8–4.5, $P < 0.001$). No difference in the rate of administration was noted for quetiapine, between mono- and polytherapy ($P = 0.697$), mono- and dual-therapy ($P = 0.466$), or dual- and polytherapy ($P = 0.91$).

Even when adjusted for baseline DOS and subtypes, the patients on polytherapy received more often received haloperidol (OR = 20.1, $P < 0.001$), pipamperone (OR = 12.4, $P < 0.001$) and benzodiazepines (OR 10.0, $P < 0.001$).

Psychopharmacological characteristics: doses and treatment duration

For patients on dual therapy, the doses of lorazepam, haloperidol and pipamperone were higher than among those on monotherapy. Conversely, no dose- differences were noted between those on dual- and polytherapy.

With respect to haloperidol dosing, patients on dual- versus monotherapy (median: 6 vs 2 mg; $P = 0.003$) and on poly- versus mono-therapy (median: 9 vs 2 mg; $P < 0.001$) received more haloperidol. For those on dual- and polytherapy, the doses of haloperidol were the same ($P = 0.86$).

Regarding pipamperone, higher doses were used in patients on dual-therapy (median: 245 mg; $P = 0.007$) and on polytherapy (median: 420 mg; $P = 0.001$) versus monotherapy (median: 220 mg). Again, no increases were noted between those on dual- and poly-therapy ($P = 0.30$).

Higher doses of lorazepam were given in dual- (median: 4.5 mg; $P = 0.003$) and poly-therapy patients (median: 6 mg; $P < 0.001$) than in those on monotherapy (median: 2 mg). There was no further increase between those on dual- and poly-therapy ($P = 0.86$).

In terms of treatment duration, there were no statistically significant differences for haloperidol ($P = 0.206$), pipamperone ($P = 0.616$) and lorazepam ($P = 0.12$) between the three drug-management approaches.

Irrespective of the multiple regimens used, doses for risperidone (median: 7.5–12.0 mg; $P = 0.36$), olanzapine (15–30 mg; $P = 0.096$) and quetiapine (125.0–337.5 mg; $P = 0.15$) were not statistically different.

Delirium resolution and severity over the course of management

In a Cox regression model, all three psychopharmacological approaches appeared inferior to supportive care only, which was associated with a delirium resolution rate of 92.5%. Notably, polytherapy achieved the lowest delirium resolution rate (60%), followed by dual (80%), and monotherapy (88.5%).

For supportive care only, the management benefit was more than three times greater than for polytherapy (BR: 3.44; $P < 0.001$), more than two times greater versus dual-therapy (BR: 2.32; $P < 0.001$), and almost two times greater versus monotherapy (BR: 1.80; $P = 0.006$) (Fig. 1, Table 2).

In the GEE model, irrespective of management approach, patients with milder baseline delirium did not show a relevant decrease in DOS scores on day 2, compared those with severe baseline delirium ($\chi^2 = 54.620$, $df = 5$, $P < 0.001$). Further, patients with severe delirium recovered more rapidly on supportive care alone than with any of the other management approaches ($\chi^2 = 43.995$, $df = 15$, $P < 0.001$).

For patients on psychotropic medications, recovery differed between those less versus more severely delirious ($P = 0.047$). In patients with mild delirium and on monotherapy, the initial decrease in delirium severity occurred on day #6 ($P < 0.001$). In those less delirious on polytherapy, delirium peaked on day 2 ($P = 0.039$) and subsequently improved. In patients with more severe delirium, more rapid recovery was noted with the initiation of management, irrespective of the approach ($P < 0.001$) (Fig. 2).

Discussion

Summary of main findings

In this observational cohort study involving 602 patients, we evaluated the role of psychotropic medications combined with supportive care versus supportive care alone in the management of delirium, and specifically compared one-, two- and poly-drug regimens. As part of routine clinical practice at our hospital, multiple regimens involving psychotropic medications were used. In total, 73 patients were managed with polytherapy, 224 with dual therapy, 227 with monotherapy, and 78 patients with supportive care alone, meaning that roughly seven out of eight patients received pharmacotherapy, whereas almost one in two received two or more psychotropic drugs.

Patients who were managed with two or more psychotropics in addition to supportive care had higher baseline delirium severity (mean DOS scores: 16.2–17.7) and they exposed the mixed subtype more often than those with lower baseline delirium severity (mean DOS score: 12.1). Patients who were managed with supportive care alone showed the best course of delirium with faster resolution than patients on pharmacological management. However, those patients had lower initial delirium severity. This indicates that mild delirium was manageable with supportive care alone. Despite combined supportive care and pharmacological management, initially severe delirious patients recovered slower and resolution rates were lower.

The pharmacological management groups differed significantly in terms of drug administration, in particular those on polytherapy. Relative to those given a single psychotropic medication, patients on polytherapy had 17.2 times the odds of receiving haloperidol, 17.2 times the odds of receiving at least one benzodiazepine, and 12.1 times the odds to receive pipamperone. Conversely, doses of lorazepam, haloperidol and pipamperone were not different between dual-therapy and polytherapy indicating that rather than adjusting the dose, further psychotropics were added.

Comparing our findings against existing guidelines and the scientific literature

The foremost step in the management of delirium is preemptive management: preventing delirium from starting in the first place [6]. Once delirium becomes manifest, identifying and eliminating as many underlying aetiologies as possible is required, and both non-pharmacological and pharmacological strategies may be employed.

Past American Psychiatric Association [21] guidelines for the treatment of delirium from 1999 recommended haloperidol as the mainstay of delirium management [12]. Conversely, the NICE guideline - published in 2010 – underlines the application of non-pharmacological management and recommends the judicious use of psychotropics for distressed patients only [13]. Although the benefits and disadvantages of these two approaches continue to be debated [22], the NICE guideline concurs with the importance of non-pharmacological, environmental, and supportive interventions - like providing a calm environment, regularly reorienting the patient, managing metabolic imbalances, reducing mind-altering medications like opioids, and providing visual and hearing aids, when necessary.

The management algorithm we used for the current study followed the APA guidelines, favouring the use of psychotropics for patients with delirium (Appendix 1), and emphasizing the use of haloperidol, pipamperone, and benzodiazepines.

Our findings support those of a pivotal study which evaluated haloperidol and risperidone versus placebo in palliative care patients [15]. In that study, neither psychopharmacological management approach matched the effectiveness of supportive care alone. The investigators concluded that placebo was superior to either haloperidol or risperidone and that antipsychotics potentially increased mortality.

The liberal administration of psychotropics in patients with delirium was recently challenged in a systematic review that incorporated 19 randomized controlled trials [23]. However, authors of another earlier systematic review of 15 randomized controlled trials came to the opposing conclusion that antipsychotics were superior to non-pharmacological management, with antipsychotics achieving higher resolution rates and decreasing overall delirium severity [24]. Patients in these two reviews were quite comparable with respect to age, amount of haloperidol used and mortality rates.

The management approach used in our study partly reflected those from a recent multicentre postal survey evaluating delirium management strategies [25]. Comparing our drug usage pattern against that of this multicentre study, across all management groups – including non-pharmacological managed patients – the rates of benzodiazepine use were 36.9% (lorazepam) and 21.9% (midazolam) versus 32.7% (diazepam); of quetiapine 12.6% versus 19.4%; and of olanzapine 2.8% versus 1.8%. Though, our patients received all immediate and consequent supportive care – versus just 45% in the multicentre study. Of note, the investigators reported preferences of treating Intensive-care units [response rate of 37.8% (165/436)] and not the actual number of treated patients.

Further, relative to a survey in which 1,384 healthcare professionals were asked about their medication preferences for patients with delirium [26], rates of benzodiazepines were similar regarding lorazepam (42.4% versus nearly 40%), whereas fewer patients received atypical antipsychotics (25% versus 40%; olanzapine, risperidone and quetiapine). The use of haloperidol was more common in these two aforementioned studies than in our own (> 80% versus 41.8%).

Although the current study sheds some light on delirium management, several questions remain unanswered. In our cohort, patients on polytherapy were more delirious at baseline and delirium severity increased towards the second day of management. One plausible explanation is that polytherapy was initiated due to these patients' more severe delirium, which alone could explain their worsening over the first 24–48 hours. On the other hand, it also is possible that the increase in delirium severity patients experienced was actually caused by their polytherapy. It also is conceivable that the worsening was caused by some other factor altogether. Unfortunately, which of these explanations is correct cannot be determined by our data.

Study strengths and limitations

This observational study had several strengths. In total, 602 inpatients were included, which makes it, to our knowledge, the largest delirium cohort study to investigate the effects of psychotropic polypharmacy on delirium resolution in a published study to date. Patients also had a broad spectrum of medical diagnoses and were recruited from diverse clinical settings. Their age and gender distribution, as well as the nature of their psychotropic management, were comparable to prior studies. Obtaining delirium scores thrice daily captured fluctuations in delirium and allowed for the identification of delirium subtypes. Recent reports also have highlighted the need for longer observation times in delirium trials [27], and our patients were followed for up to twenty days.

Despite these study strengths, several limitations must be noted. First, due to the study's design, patients were not enrolled until the delirium manifested. That is why there was no basal cognitive assessment and no screening for dementia. According to the evaluation of patient records, there was no difference in the prevalence of dementia between groups. The actual extent of mild to moderate cognitive impairment in this cohort might be underestimated, however. The presence of cognitive impairment is of importance for both the course of delirium and the effect of psychotropic medication.

Then, pipamperone is rarely used outside Germany and Switzerland and may not be relevant for some audiences. It is low-potency antipsychotic, an antagonist of 5HT_{2A-C}, D₂₋₄ and α_{1-2} -receptors with much higher activity against the D₄ and 5HT_{2A} than D₂ receptor and insignificant activity against histamine₁- and muscarinic-anticholinergic receptors [28].

Even though benzodiazepines were administered in a considerable number of patients in our cohort, it is usually not considered a first line treatment in the pharmacological management of delirium. On the contrary, benzodiazepine administration might be a significant risk factor for delirium. Therefore, benzodiazepine administration might have confounded antipsychotic treatment and even worsen delirium.

Most importantly, since our patients were not randomised to their treatment groups, it may be that group allocation bias was an issue, with those in the polytherapy group destined to do worse primarily on the basis of their delirium severity, rather than their treatment being less effective. Similarly, it may be that those who were treated non-pharmacologically were so for various reasons, including the treatment team's expectations of patient recovery. One finding

against this latter argument is that our patients with severe baseline delirium improved significantly more with non-drug than drug therapy. Why this is so clearly warrants further study. In the end, further randomised controlled clinical trials assessing delirium management are required to clarify the role of psychotropic and non-psychotropic therapies in delirium management.

Conclusions

The management of patients with delirium is challenging, particularly of those patients with severe delirium. This study provides further information on delirium management approaches and appears to

favour supportive care alone in mild delirium, as well as the judicious, rather than routine, use of psychotropics. Certainly, patients in severe distress require psychotropics. In our cohort, physicians tend to add new substance classes instead of increasing the dosages of those drugs already administered; this strategy did not improve delirium management in terms of resolution rates and duration. In some instances, optimising the dose of the psychotropic drugs already being used, rather than adding new ones, might be prudent in seemingly treatment-resistant patients. Our findings indicate that patients with severe delirium are prone to receive more psychotropic medication and that those patients, despite supportive and pharmacological management, suffer longer from delirium. Therefore, strategies for patients with severe delirium are highly requested. Randomised clinical trials for the investigation of no-drug, single-drug, dual-drug and poly-drug therapy remain necessary.

Abbreviations

DOS Delirium Observation Screening Scale, LOS Length of stay

Declarations

Ethics approval and consent to participate

All participants provided written informed consent. The study protocol was approved by the ethics committee of the Canton of Zurich (KEK-ZH-Nr. PB-2016-01264). All participants provided written informed consent.

Consent to publish

All participants provided written informed consent.

Availability of data and materials

The authors confirm that the data supporting the findings of this study are available within the article.

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable

Authors' Contributions

CMZ and SB devised the project, performed the statistical analyses including data interpretation and authored the manuscript which was commented by MS, RvK, PH, PP and SK. CMZ, SB, PH, SK were in charge of databank management. All co-authors provided critical feedback on the final manuscript.

Acknowledgements

Not applicable

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th edition, Text Revision. Washington, DC, American Psychiatric Association. 124-127. 2000. 2000.
2. Maldonado JR. Acute Brain Failure: Pathophysiology, Diagnosis, Management, and Sequelae of Delirium. *Critical care clinics*. 2017;33(3):461-519.
3. Zipser CM, Deuel J, Ernst J, Schubert M, von Kanel R, Bottger S. The predisposing and precipitating risk factors for delirium in neurosurgery: a prospective cohort study of 949 patients. *Acta Neurochir (Wien)*. 2019.
4. Zipser CM, Deuel J, Ernst J, Schubert M, Weller M, von Kanel R, et al. Predisposing and precipitating factors for delirium in neurology: a prospective cohort study of 1487 patients. *Journal of neurology*. 2019.
5. Smulter N, Lingehall HC, Gustafson Y, Olofsson B, Engstrom KG. Delirium after cardiac surgery: incidence and risk factors. *Interactive cardiovascular and thoracic surgery*. 2013;17(5):790-6.
6. Oh ES, Fong TG, Hshieh TT, Inouye SK. Delirium in Older Persons: Advances in Diagnosis and Treatment. *Jama*. 2017;318(12):1161-74.
7. Koster S, Hensens AG, van der Palen J. The long-term cognitive and functional outcomes of postoperative delirium after cardiac surgery. *Ann Thorac Surg*. 2009;87(5):1469-74.
8. Fong TG, Davis D, Growdon ME, Albuquerque A, Inouye SK. The interface between delirium and dementia in elderly adults. *The Lancet Neurology*. 2015;14(8):823-32.
9. Moskowitz EE, Overbey DM, Jones TS, Jones EL, Arcomano TR, Moore JT, et al. Post-operative delirium is associated with increased 5-year mortality. *Am J Surg*. 2017;214(6):1036-8.
10. Barr J, Fraser GL, Puntillo K, Ely EW, Gelinas C, Dasta JF, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Critical care medicine*. 2013;41(1):263-306.
11. Pandharipande P, Ely EW. Sedative and analgesic medications: risk factors for delirium and sleep disturbances in the critically ill. *Critical care clinics*. 2006;22(2):313-27, vii.
12. Trzepacz PTB, W.; Franklin, J.; Levenson, J.; Martini, R.; Wang, P. Practice guideline for the treatment of patients with delirium. American Psychiatric Association. . *The American journal of psychiatry*. 1999;156((5 Suppl)):1-20.
13. National Clinical Guideline C. National Institute for Health and Clinical Excellence: Guidance. Delirium: Diagnosis, Prevention and Management. London: Royal College of Physicians (UK) National Clinical Guideline Centre - Acute and Chronic Conditions.; 2010.

14. Girard TD, Exline MC, Carson SS, Hough CL, Rock P, Gong MN, et al. Haloperidol and Ziprasidone for Treatment of Delirium in Critical Illness. *The New England journal of medicine*. 2018.
15. Agar MR, Lawlor PG, Quinn S, Draper B, Caplan GA, Rowett D, et al. Efficacy of Oral Risperidone, Haloperidol, or Placebo for Symptoms of Delirium Among Patients in Palliative Care: A Randomized Clinical Trial. *JAMA internal medicine*. 2017;177(1):34-42.
16. Herzig SJ, Rothberg MB, Guess JR, Stevens JP, Marshall J, Gurwitz JH, et al. Antipsychotic Use in Hospitalized Adults: Rates, Indications, and Predictors. *Journal of the American Geriatrics Society*. 2016;64(2):299-305.
17. Vandenberg JP, von Elm E, Altman DG, Gøtzsche PC, Vandenbroucke JP, Pocock SJ, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Epidemiology (Cambridge, Mass)*. 2007;18(6):805-35.
18. Schuurmans MJ, Shortridge-Baggett LM, Duursma SA. The Delirium Observation Screening Scale: a screening instrument for delirium. *Research and theory for nursing practice*. 2003;17(1):31-50.
19. Lipowski ZJ. Transient cognitive disorders (delirium, acute confusional states) in the elderly. *Am J Psychiatry*. 1983;140(11):1426-36.
20. Taulbee LR, Folsom JC. Reality orientation for geriatric patients. *Hospital & community psychiatry*. 1966;17(5):133-5.
21. Wildes TS, Winter AC, Maybrier HR, Mickle AM, Lenze EJ, Stark S, et al. Protocol for the Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes (ENGAGES) study: a pragmatic, randomised clinical trial. *BMJ open*. 2016;6(6):e011505.
22. Meagher D, Agar MR, Teodorczuk A. Debate article: Antipsychotic medications are clinically useful for the treatment of delirium. *International journal of geriatric psychiatry*. 2017.
23. Neufeld KJ, Yue J, Robinson TN, Inouye SK, Needham DM. Antipsychotic Medication for Prevention and Treatment of Delirium in Hospitalized Adults: A Systematic Review and Meta-Analysis. *Journal of the American Geriatrics Society*. 2016;64(4):705-14.
24. Kishi T, Hirota T, Matsunaga S, Iwata N. Antipsychotic medications for the treatment of delirium: a systematic review and meta-analysis of randomised controlled trials. *Journal of neurology, neurosurgery, and psychiatry*. 2016;87(7):767-74.
25. Kotfis K, Zegan-Baranska M, Zukowski M, Kusza K, Kaczmarczyk M, Ely EW. Multicenter assessment of sedation and delirium practices in the intensive care units in Poland - is this common practice in Eastern Europe? *BMC anesthesiology*. 2017;17(1):120.
26. Patel RP, Gambrell M, Speroff T, Scott TA, Pun BT, Okahashi J, et al. Delirium and sedation in the intensive care unit: survey of behaviors and attitudes of 1384 healthcare professionals. *Critical care medicine*. 2009;37(3):825-32.
27. Bush SH, Kanji S, Pereira JL, Davis DHJ, Currow DC, Meagher D, et al. Treating an established episode of delirium in palliative care: expert opinion and review of the current evidence base with recommendations for future development. *Journal of pain and symptom management*. 2014;48(2):231-48.

Figures

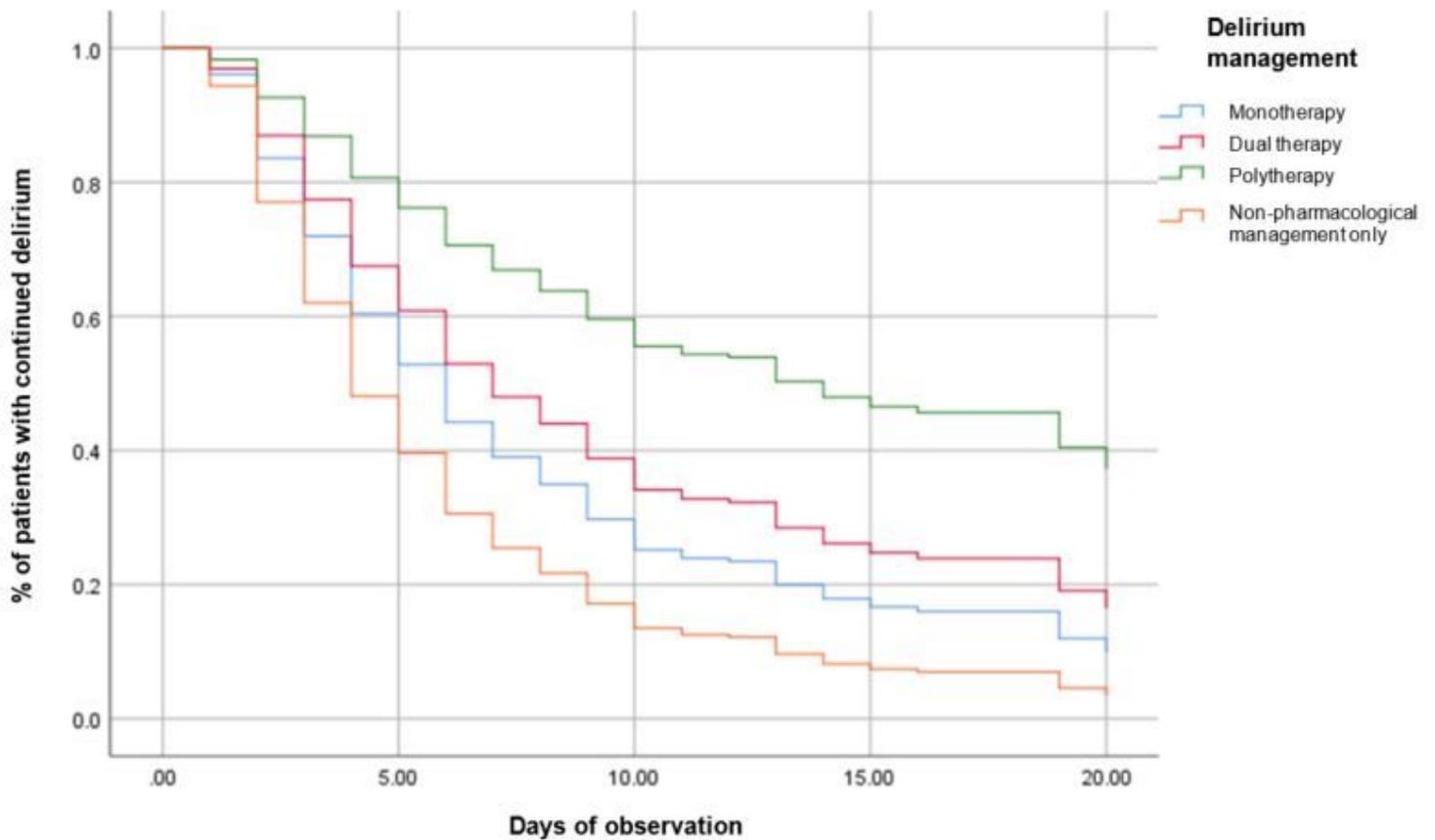


Figure 1

Cox Regression model to evaluate pharmacological management of delirium. The y-axis shows the percentage of patients with continued delirium; the x-axis shows the days of observation. Curves for the four medical regimens are depicted: monotherapy (blue), dual therapy (red), poly-therapy (yellow), and non-pharmacological management only (magenta). Curves for the three drug-therapy groups all indicate significantly less delirium resolution than with non-pharmacological management only. The initial Delirium Observation Screening (DOS) score was set as a covariate.

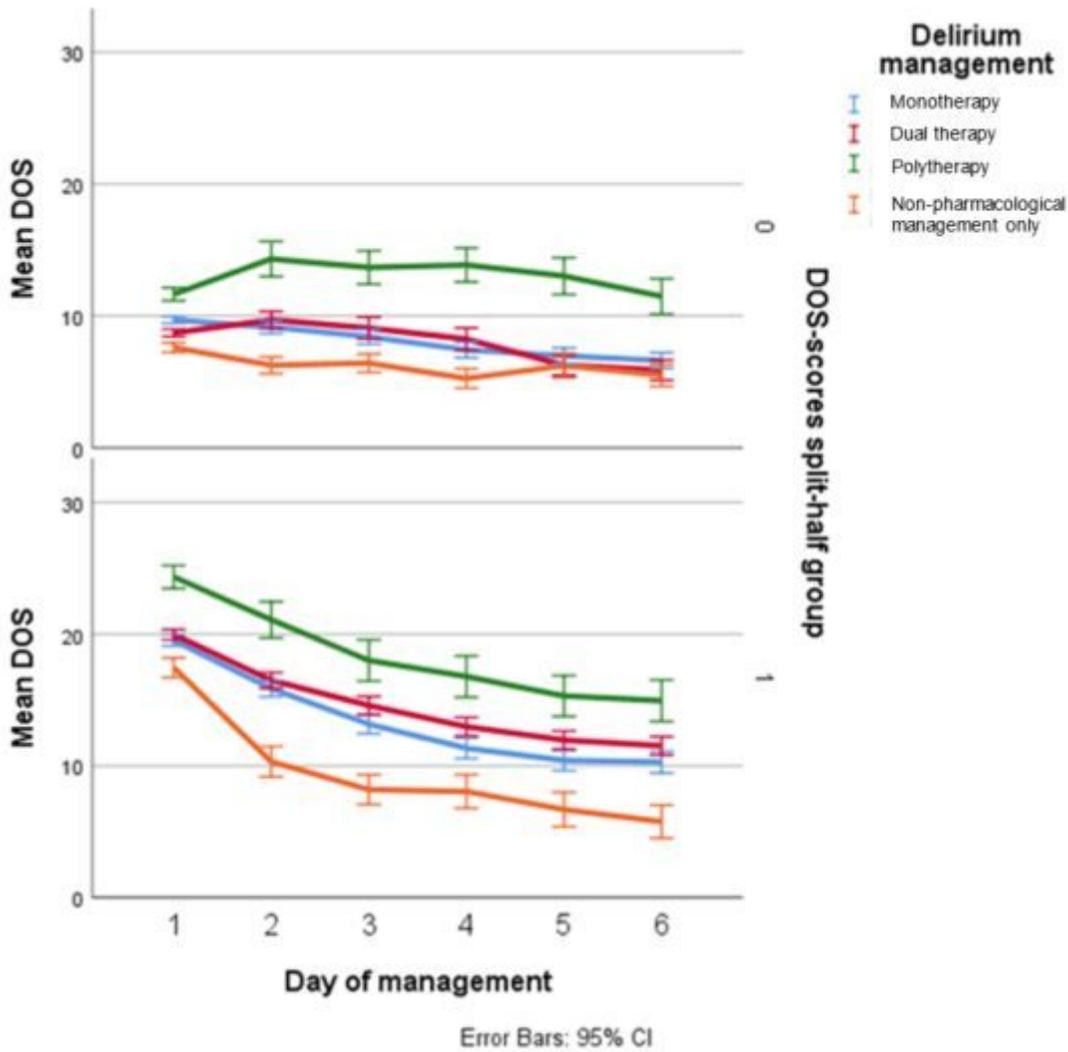


Figure 2

Generalized estimating equation (GEE) models for the four delirium-management regimens. The upper graph depicts the half of patients with lower mean baseline Delirium Observation Screening (DOS) scores; the lower graph, those patients with higher delirium scores. For patients with higher initial delirium severity, DOS scores fell more rapidly than among patients with lower baseline scores.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [DelirPolypharmacyAPPENDIX1FINAL.docx](#)