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Review article

Intravenous haloperidol: A systematic review of side effects and recommendations for clinical use

Scott R. Beach[a,*], Anne F. Gross[b], Kimberly E. Hartney[c], John B. Taylor[a], James R. Rundell[d]

[a] Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, Boston, MA, United States of America
[b] Department of Psychiatry, Oregon Health & Science University, Portland, OR, United States of America
[c] Department of Psychiatry, University of South Florida, Tampa, FL, United States of America
[d] Department of Psychiatry, Uniformed Services University of the Health Sciences School of Medicine, Bethesda, MD, United States of America

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ABSTRACT

Introduction: Though not approved by the United States Food and Drug Administration, intravenous haloperidol (IVH) is widely used off-label to manage agitation and psychosis in patients with delirium in the hospital setting. Over the years, concerns have emerged regarding side effects of IVH, particularly its potential to cause QT prolongation, torsades de pointes (TdP), extrapyramidal symptoms and catatonia.
Methods: We conducted a systematic review of literature of published literature related to side effects of IVH in PubMed in accordance with PRISMA guidelines.
Results: 77 of 196 identified manuscripts met inclusion criteria, including 34 clinical trials and 34 case reports or series.
Discussion: Extrapyramidal symptoms, catatonia and neuroleptic malignant syndrome appears to be relatively rare with IVH. In most prospective studies, IVH did not cause greater QT prolongation than placebo, and rates of TdP with IVH appear to be low. There is not clear evidence to suggest that IVH carries greater risk for QT prolongation or TdP than other antipsychotics.
Conclusions: Based on the available literature, we provide modified evidence-based monitoring recommendations for clinicians prescribing IVH in hospital settings. Specifically, we recommend electrocardiogram monitoring only when using doses > 5 mg of IVH and telemetry only for high-risk patients receiving cumulative doses of at least 100 mg or with accurately corrected QTc > 500 ms.

1. Introduction

On February 11, 1958, R1625 (haloperidol), was synthesized by Janssen Pharmaceuticals in Belgium as the forty-fifth butyrophenone, a new chemical family intended to be used as analgesics [1,2]. Found to be more powerful as a sedative than as an analgesic in mice, haloperidol was administered intravenously to patients at Liege hospital five weeks after its discovery [1]. The first report using haloperidol in 18 patients with psychomotor agitation highlighted “sedation without sleep” and its ability to “allow a psychotherapeutic contact subsequent to the injection” [1,3].

Since that time, the intravenous form of haloperidol (IVH) has come to be widely used in medical and surgical settings to manage patients with delirium and agitation, and is one of the few such medications available by the intravenous route. Initial reports of IVH for managing agitation and psychosis in medically-ill patients supported its safety in cardiac patients. Hasse and colleagues recommended IVH over the intramuscular (IM) form specifically due to a propensity for less cardiac stress [4]. In 1976, IVH use was reported in the first post-myocardial infarction patient, and in 1978 its use was reported in a patient with cardiac dysrhythmia [5].

By 1978, IVH was being used to manage the sequelae of delirium. At the American Psychiatric Association's (APA's) Annual Meeting that year, Dudley and colleagues presented their experience using IVH in 20 patients who were hospitalized with life threatening medical conditions [5]. In every case, sufficient reversal of agitation was rapidly achieved in order to obtain appropriate diagnostic or therapeutic interventions. Cassem and Sos presented their findings at the same meeting on the use of IVH in post-operative patients undergoing cardiac surgery and in post-myocardial infarction patients, using single doses up to 185 mg [6]. The IV route was selected due to concerns about pain and fear caused from repeated IM injections, the potential for repeated IM

* Corresponding author at: Department of Psychiatry, Massachusetts General Hospital, 55 Fruit Street/Warren 605, United States of America.
E-mail address: sbeach1@partners.org (S.R. Beach).

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injections to elevate levels of creatinine kinase, and a desire to avoid IM injections in patients with compromised peripheral perfusion, in whom IM injections may lead to unreliable absorption from muscle. The authors reported that IVH had little effect on blood pressure and heart rate, worked rapidly, and did not cause extrapyramidal symptoms (EPS).

As the popularity of IVH grew, consultation-liaison (CL) psychiatrists began to report tolerability at a wide range of doses. Fernandez and colleagues described the use of continuous IVH infusion (or "Haldol drip") for the management of severe agitation [7]. In 1991 Sanders and colleagues published on the use of 1200 mg IVH within 24 h for a patient with agitated delirium following intra-aortic balloon pump placement [8], and in 1995 Levenson published on the use of 1155 mg IVH within 24 h and 2842 mg IVH within four days for a patient with agitated delirium following lung transplant [9]. All cases reported no adverse effects.

In 1999 the APA created practice guidelines for the treatment of delirium and cited haloperidol and droperidol as the "safest and most effective antipsychotics for delirium" [10]. Though second-generation antipsychotics have been increasingly employed over the past two decades, IVH has remained the first-line pharmacological agent in many centers for managing delirium, likely due to its pharmacokinetic and receptor profile properties [11]. IVH is twice as potent as the oral form (due to extensive first-pass oral metabolism), and the time to onset of IVH is faster than both oral and IM administration [12]. Furthermore, the mean half-life is 14 h, producing a long-lasting effect (though shorter than oral or IM forms) [13–16]. Haloperidol has high binding affinity for dopamine (D2) receptors, with little effect on serotonergic, alpha, histamine, or cholinergic receptors. Haloperidol is also a sigma-1 receptor antagonist, which distinguishes it from other antipsychotic agents [17].

Despite its widespread use and initially reported favorable safety profile, the FDA has never approved IVH for use. Furthermore, IVH has gained a reputation over the past several decades for causing untoward side effects. The association of haloperidol with prolongation of the QT (or rate-corrected QTc) interval and torsade de pointes (TdP) was first reported in 1983 with the use of high-dose oral haloperidol [18]. In 1988, Huyse published the first reported case of cardiac arrest following the use of IVH [19], and in 1992 Rettmar documented the first case of known TdP with IVH, which was followed shortly afterwards by the first case series reported in the United States [20,21]. These concerns culminated in a 2007 warning by the Food and Drug Administration regarding the potential for QT prolongation and TdP with IVH, which recommended telemetry for any patients receiving IVH [22]. Additionally, many physicians worry about the potential for IVH to cause catatonia, neuroleptic malignant syndrome (NMS), and EPS such as dystonic reactions, akathisia, and parkinsonism.

Concerns about side effects are based largely on case reports and case series, and it is challenging to estimate the exact prevalence of these events. Accordingly, we set out to conduct a systematic review of the literature with regards to the side effect profile of IVH. In doing so, we aimed to generate updated recommendations regarding its use that are based on the full body of evidence available.

2. Methods

The guidelines and criteria outlined in Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) were followed and applied to ensure proper reporting of the data [23] (see Supplementary Fig. 1). A systematic literature search was conducted using keyword-based queries in the PubMed electronic database, first in October 2019 and again in May 2020 to include more recent articles. It was limited to humans and included articles from 1958, when the use of IVH was first described, until May 1, 2020.

Search terms included "IV Haldol," "IV haloperidol," "intravenous haldol," "intravenous haloperidol," "parenteral haldol," or "parenteral haloperidol." In order to ensure articles were not missed, "haloperidol" was also searched in combination with the following terms: "QT," "torsades," "extrapyramidal," "dystonia," "akathisia," "catatonia," and "malignant." Articles identified in this systematic search were imported into a standard reference manager, EndNote X9 (Thomson Reuters, 2019).

In the first round of assessment, one study team member (SB) performed automated searches of the database as discussed above, removed duplicate articles, and screened titles and abstracts of the remaining articles to rule out excluded studies. During the second round of review, full texts were read and reviewed for eligibility criteria by SB, with clarification by a second author (AG) as needed. Attempts were made to contact authors if the full article was not immediately available. Reviewers also searched the reference lists of eligible manuscripts to identify other possible articles. Articles were included if they 1) described the use of IVH in human subjects, 2) reported use in subjects 18 years or older, and 3) included information on any side effects, including QT prolongation, TdP, dystonia, akathisia, parkinsonism, tardive dyskinesia, catatonia, or NMS. Data for studies examining QT prolongation and EPS with IVH was extracted, including number of subjects, study population, comparator, dose, and outcomes.

3. Results

A PRISMA Diagram [23] is shown in Supplementary Fig. 2. 196 unique abstracts were initially identified, of which 28 were excluded as not involving IVH or pertaining to animal models based on title or abstract prior to article review. 168 articles were screened in full. 71 articles met inclusion criteria, and an additional 6 articles were identified through review of references. Of the 77 articles included in the final review, 22 reported on EPS, catatonia or NMS and 59 reported on QT prolongation or TdP with IVH (4 articles reported on both side effects). Of the 23 articles describing EPS, NMS or catatonia, 11 were clinical trials [24–34] and 12 were case reports or series [5,6,14,35–43]. Of the 59 articles related to QT prolongation or TdP, 28 were clinical trials (of which 18 directly assessed rates of QT prolongation or TdP with IVH) [12,16,24,25,29,33,34,44–64], 22 were case reports or case series [8,9,20,21,55,57,65–80], and 9 were reviews [13,15,81–87].

Table 1 shows 11 cases of EPS, NMS or catatonia reported in 8 articles. Three case series noted no instances of EPS in at least 30 patients treated with IVH [5,6,88]. Three articles reported 5 cases of EPS [14,35,37]. Total doses ranged from 50 to 1500 mg (over hours to days), and at least one of the patients also received large doses of IM haloperidol [35]. One series noted "mild EPS" only in 3 of 16 patients treated and did not provide demographic information or note other medications or confounding factors [37]. Of note, an additional case series from 1963 involving 120 patients reported 40 instances of dystonic reactions with IVH [43].

IVH was associated with NMS in 4 case reports [36,38,40,42]. All cases involved men, with ages ranging from 19 to 48 years. Total IVH dose ranged from 20 to 800 mg. 3 of the 5 cases involved patients with head injury, 1 patient also received droperidol, and another was suffering from alcohol withdrawal. Only one case appeared to involve a patient without other obvious risk factors for NMS [40]. Only one case series, featuring two cases, associated IVH with catatonia [39]. Both cases also involved abrupt discontinuation or taper of other antipsychotics agents.

The case report literature connecting IVH to QT prolongation and TdP has previously been summarized and outlined in table form [86]. Our search yielded only one additional report that was not included in that systematic review [78]. Several reports did mention cases in which IVH had no effect on QT [7–9,80].

Table 2 outlines clinical trials for which information on rates of QT prolongation, TdP or EPS was directly reported. Among four recent prospective studies involving a total of over 1200 patients, three

Table 1
Cases of EPS, NMS or catatonia with IVH.

Year	First author	Age	Gender	Total dose (mg)	Indication	Other medications received in the same time frame	Risk or confounding factors	Outcome
1976	Dencker – Case 1 [37]	Unknown	Unknown	> 50 in single dose	Unknown (mentions alcohol withdrawal and schizophrenia)	Unknown	Unknown	"Mild EPS"
1976	Dencker – Case 2 [37]	Unknown	Unknown	> 50 in single dose	Unknown (mentions alcohol withdrawal and schizophrenia)	Unknown	Unknown	"Mild EPS"
1976	Dencker – Case 3 [37]	Unknown	Unknown	> 50 in single dose	Unknown (mentions alcohol withdrawal and schizophrenia)	Unknown	Unknown	"Mild EPS"
1984	Andersson [14]	20	Male	1500 (dose of 10 mg nightly at time of EPS)	Delirium	Methotrexate, prednisone, lorazepam, methotrimeprazine	Young male, use of methotrimeprazine	"EPS"
1990	Levitt [40]	33	Male	45	Delirium	None listed	Recent surgery	NMS
1995	Burke [36]	38	Male	> 780	Delirium	Lorazepam, clomipramine, paroxetine, Propofol, droperidol	Possible traumatic brain injury (TBI), use of droperidol	NMS
1997	Blitzstein [35]	55	Female	910	Delirium	IM haloperidol (108 mg), Buspirone	IM haloperidol	Parkinsonism
2011	Shaikh [42]	19	Male	20	Delirium	"Antibiotics"	Young male, TBI	NMS
2012	Gugger – Case 1 [39]	48	Female	30	Schizoaffective disorder	Heparin, lamotrigine, pantoprazole	Abrupt cessation of clozapine, paroxetine and diphenhydramine; schizoaffective disorder	Catatonia
2012	Gugger – Case 2 [39]	38	Male	24	Schizoaffective disorder	Lorazepam, quetiapine, aripiprazole, mirtazapine, venlafaxine, zolpidem, atenolol, tamsulosin, docusate, midazolam, propofol, cefazolin, ephedrine, morphine, fentanyl, remifentanil, succinylcholine, dexamethasone, phenylephrine, ondansetron	Surgery; schizoaffective disorder; Use of corticosteroids; Abrupt reduction of quetiapine	Catatonia
2013	Dixit [38]	48	Male	800	Alcohol withdrawal delirium	Vancomycin, cefepime, lorazepam, fentanyl, linezolid, meropenem, famotidine	Alcohol withdrawal	NMS

demonstrated no increased rates of EPS with IVH compared to placebo (with two actually showing fewer cases of EPS in the IVH group), and the fourth reported no EPS in 45 patients treated with IVH [24,29,33,34].

Ten of eleven prospective studies, involving a total of 1522 patients treated with up to 20 mg daily of IVH and including 6 placebo-controlled studies, found no evidence of QT prolongation with IVH [24,25,29,33,34,45–49,53,58,89]. One prospective study reported 9/177 patients developed "marginal QT prolongation" with IVH [58]. Two retrospective studies demonstrated no QT prolongation with IVH [44,54], and a third suggested no higher rates of TdP incident reporting compared to other antipsychotics [50]. Two retrospective studies found higher rates of QT prolongation with IVH and one reported several instances of TdP [49,52,55,57].

4. Discussion

4.1. IVH and EPS

Aside from sporadic case reports, concerns regarding IVH and EPS appear to stem from 3 main sources. The 1963 case series reported that 40/120 patients with schizophrenia developed dystonic reactions after receiving 10 mg IVH, but provided no other information about these patients and also mentioned giving patients in the study IM haloperidol on alternating days, making it challenging to draw meaningful conclusions [43]. A 1985 prospective trial involving healthy subjects without psychiatric illness noted dystonia in 4 of 12 subjects receiving IVH and akathisia in 8 of 12 [30]. A 1989 prospective study of 38 terminally-ill patients with acquired immunodeficiency syndrome (AIDS) found that 17 demonstrated EPS after IVH 10 mg given in combination with lorazepam [27]. It is worth noting that patients with AIDS are at increased risk for EPS at baseline due to the virus's effects on the basal ganglia and subcortical structures, suggesting a vulnerable population at baseline. Despite these reports, the overwhelming body of literature, including all recent placebo-controlled trials, suggests that the risk of EPS with IVH is very low [5,6,26,28,31,32,43,88].

There have been several theories offered for IVH causing low rates of EPS [14,37]. Some have suggested that patients receive IVH primarily to manage delirium, which may represent a state of relative cholinergic deficit and therefore protect from EPS [31]. Alternatively, Menza also proposed that because IVH avoids first pass metabolism, levels of its metabolite, Reduced Haloperidol, may be lower in the striatum [31].

With regards to monitoring for EPS, including akathisia, parkinsonism and dystonias, assessment should be continued given the non-invasive nature of the exam. One study suggests that EPS is most likely to emerge early (within 2 h) or late (24–48 h) after administration [30]. If EPS is noted with the use of IVH, the medication should not be reflexively stopped unless the EPS is severe. If mild, a careful risk-benefit analysis should be conducted that takes into account the risk of agitation and also considers potential alternative agents. It is worth noting, however, that there is no clear evidence suggesting that the risk of EPS with IVH is more or less than that with atypical antipsychotics.

4.2. Catatonia and NMS

Though not technically EPS, neuroleptic malignant syndrome (NMS) and catatonia are sometimes considered related syndromes based on their representing states of dopamine depletion. Though parenteral neuroleptics are commonly listed as a risk factor for NMS, the literature supporting this is almost based entirely on IM, rather than IV, formulations [42,90,91]. Taken together, the cases reviewed here indicate that NMS or catatonia can occur with IVH, though the frequency of reported cases in the literature appears lower than seen with IM or oral formulations of haloperidol, and lower than that seen with most other neuroleptics. Perhaps this is similar to the lower frequency

Table 2
Studies examining EPS and QT prolongation with IVH.

Reference	Type of study	Comparator	Number of subjects receiving IVH included in analysis (n)	Study population	Dose of IVH	Conclusions
EPS						
Van den Boogaard 2018 [34]	Randomized, double-blind trial	Placebo	1082	Critically-ill patients	1-2 mg q8h	No difference in rates of EPS between IVH and placebo
Al-Qadheeb 2016; Duprey 2016 [24,25]	Randomized, double-blind, placebo-controlled trial	Placebo	34	Mechanically-ventilated patients with subsyndromal delirium	1 mg q6h	No difference in rates of EPS between IVH and placebo
Page 2013 [33]	Randomized, double-blind, placebo-controlled trial	Placebo	71	Mechanically-ventilated delirious patients	2.5 mg q8h	No difference in rates of EPS between IVH and placebo
Lee 2007 [29]	Randomized, double-blind trial	Ondansetron	45	Females undergoing surgery	2 mg × 1	No EPS reported with IVH
Fernandez 1989 [27]	Open-label, prospective trial	None	38	Male patients with AIDS and delirium	12–142 mg (Mean = 42 mg)	17 patients (44.7%) developed EPS
Menza 1988 [32]	Open-label, prospective trial	None	18	Hospitalized patients	Mean = 16.4 mg/day	1 case of "very mild Parkinsonism" noted
Menza 1987 [31]	Prospective single-blind trial	Oral haloperidol	4	Hospitalized patients	Mean = 10.1 mg/day	Less severe EPS in IVH compared to oral haloperidol; 2 subjects developed akathisia with IVH
Magliozzi 1985 [30]	Open-label, prospective trial	Oral haloperidol	12	Healthy male volunteers	0.125 mg/kg	Dystonia in 4 subjects; akathisia in 8 subjects
Grunberg 1984 [28]	Randomized, double-blind, cross-over trial	Metoclopramide	33	Patients receiving chemotherapy	15	1 subject developed EPS
Dyrberg 1962 [26]	Double-blind, placebo-controlled trial	Placebo	548	Patients undergoing elective surgery	5 mg × 1	No EPS reported with IVH
QT or TdP						
Burbuque 2020 [44]	Retrospective cohort trial	Oral haloperidol	63	Critically-ill patients	2–13 mg (mean = 4.35)	The number of patients with long QT did not increase with IVH; No dose-dependent effect; no differences between IVH and oral haloperidol
Girard 2018 [47]	Prospective, randomized, double-blind, placebo-controlled trial	Placebo, ziprasidone	189	Critically-ill delirious patients	20 mg daily	No significant difference in rates of QT prolongation between IVH and placebo; QT prolongation more common in ziprasidone than in IVH or placebo
van den Boogaard 2018 [34]	Prospective, randomized, double-blind trial	Placebo	1082	Critically-ill patients	1-2 mg q8h	No difference in final QTc compared to placebo group and fewer discontinuations in IVH group due to QT prolongation
Al-Qadheeb 2016; Duprey 2016 [24,25]	Prospective, randomized, double-blind, placebo-controlled trial	Placebo	34	Mechanically-ventilated patients with subsyndromal delirium	1 mg q6h	No differences in average maximum QTc or rates of QT prolongation when compared to placebo
Gaffigan 2015 [46]	Prospective, randomized, double-blind trial	Metoclopramide	14	Patients with migraine headache	5 mg × 1	No significant change in QTc during treatment and no significant difference in final QTc compared with metoclopramide
Scharfetter 2014 [54]	Retrospective cohort trial	Lorazepam	64	Patients with acute psychosis	Unknown	IVH alone did not cause greater QT prolongation than lorazepam
van den Boogaard 2013 [58]	Prospective, case-control trial	No treatment	177	Critically-ill patients at high risk for delirium	1 mg q8h	IVH was stopped in 9 patients due to "marginal QT prolongation" (not defined); no arrhythmias noted
Page 2013 [33]	Prospective, randomized, double-blind, placebo-controlled trial	Placebo	71	Mechanically-ventilated delirious patients	2.5 mg q8h	No significant difference in rates of QT prolongation > 500 ms compared to placebo; no episodes of TdP
Meyer-Mazetti 2011 [50]	Retrospective analysis of data reporting system	Oral haloperidol, olanzapine, quetiapine	83	Patients in World Health Organization Drug Reporting Database	〈2−〉 100 mg	IVH is not associated with more frequent reporting of TdP than olanzapine or quetiapine
Ozeki 2010 [52]	Retrospective analysis	Other antipsychotics	47	Inpatients with schizophrenia	Doses not provided (dose of 2 mg used in analysis)	IVH is associated with higher rates of QT prolongation than other antipsychotics
Reade 2009 [53]	Prospective, randomized, open-label, parallel groups, pilot trial	Dexmedetomidine	10	Mechanically-ventilated delirious patients	Optional loading dose of 2.5 mg followed by 0.5–2 mg/h	No significant difference in change in QTc or rates of abnormal QT interval compared to dexmedetomidine

(*continued on next page*)

Table 2 (*continued*)

Reference	Type of study	Comparator	Number of subjects receiving IVH included in analysis (n)	Study population	Dose of IVH	Conclusions
Chu 2008 [45]	Prospective, randomized, double-blind, placebo- and positive-control trial	Saline, droperidol, dexamethasone	146	Women undergoing vaginal hysterectomy	2 mg × 1	No significant difference in final QTc or rates of QT prolongation compared to saline infusion
Grecu 2008 [48]	Prospective, randomized, double-blind trial	Ondansetron	133	Patients undergoing general anesthesia	1 mg × 1	No significant differences in rates of QT prolongation or change in QT when IVH given with ondansetron, compared with ondansetron alone
Lee 2007 [29]	Prospective, randomized, double-blind trial	Ondansetron	45	Females undergoing surgery	2 mg × 1	No difference in final QTc compared to ondansetron and no instances of QT prolongation in IVH group
Hatta 2001 [49]	Retrospective, cross-sectional cohort trial	Flunitrazepam alone (vs. flunitrazepam and IVH)	34	Patients in psychiatric emergency room	Mean dose 17.6 mg (dose range not given)	No difference in QTc in patients receiving IVH and flunitrazepam compared to those only receiving flunitrazepam immediately after IVH, but IVH caused greater change in QTc and higher rates of QT prolongation 8 h later
Tisdale 2001; Sharma 1998 [55,57]	Retrospective, case-control trial	None	223	Critically-ill patients	Mean = 49.6 mg	8 patients developed TdP; the odds of developing TdP were greatest in patients with QTc > 521 ms; Patients receiving > 35 mg/day were at highest risk

of EPS with IVH, given the connections between catatonia and parkinsonism in particular [92]. It is also worth noting that most cases involved other significant risk factors, including abrupt cessation of clozapine or traumatic brain injury [93–95]. Physicians should be aware of the potential risk and accordingly monitor patients for emerging symptoms.

4.3. IVH, QT prolongation and TdP

In 1992, Rettmar documented the first case of known TdP with IVH, which was followed shortly afterwards by the first case series reported in the United States [20,21]. A 2010 systematic review included 54 reports of TdP and 58 reports of QT prolongation with IVH, but only reported a single death [8,20,21,55,57,65–77,79]. The data from this review and more recent studies can be used to start to answer some of the common questions posed to psychiatrists.

4.3.1. To what extent does IVH cause QT prolongation and is it dose-dependent?

The majority of studies reviewed do not demonstrate QT prolongation with IVH [24,25,29,33,34,44–48,53,54]. Three reports suggest, however, that IVH has the potential to cause QT prolongation under certain circumstances [49,52,58]. In the first, 9 of 177 subjects had "marginal QT prolongation," but the extent of QT prolongation was not defined, and there were no comparisons made to the control group [58]. In the second, 34 patients treated with flunitrazepam followed by IVH had longer QT by an average of 9 ms compared with those receiving flunitrazepam alone [49]. The change in QT moderately correlated with dose, with 2 patients displaying an increase of > 100 ms following a dose of > 25 mg. Finally, a retrospective study found IVH associated with a higher rate of QT prolongation (defined as > 470 ms in men and > 480 ms in women) than other antipsychotics (RR = 1.29, 95% CI 1.18, 1.43) [52]. In all three studies, QT prolongation was mostly mild and of unclear clinical significance. It is worth noting that a commonly cited source for the claim that IVH prolongs the QT interval is an unpublished observational study from 1995 involving 6 patients that was never subject to peer review [85].

The potential for QT prolongation with IVH to be dose-related is mainly supported by the 2010 systematic review, in which 80% of patients with QT prolongation or TdP received > 10 mg IVH [86]. No thorough QT study has been conducted with IVH.

4.3.2. What is the relationship between IVH and TdP?

Besides the 2010 systematic review, the only study to suggest that TdP may be more likely with IVH at higher doses is a 1998 study that examined 268 patients who received IVH over the course of a year [55,57]. 8 patients (3.6%) developed TdP after receiving IVH and were compared to 40 controls who did not develop TdP. The TdP group was more likely to have received > 35 mg IVH in the 24 h before the event (33.3% vs. 3.6%, $p < .001$). Further analysis revealed that TdP occurred in 7 of 11 patients who received > 35 mg IVH in < 6 h but in 0 of 10 patients who received > 35 mg IVH over 6–24 h. No deaths were reported in any patients.

4.3.3. Who is at risk for TdP with IVH?

One area of consistency in the literature is that the vast majority of patients who develop TdP with IVH have other risk factors. Of the 70 cases of QT prolongation or TdP in the systematic review, 68 had documented other associated risk factors (including critical illness, cardiac disease and other QT-prolonging medications) [86]. 96% of patients with TdP had QTc > 450 ms at the time of the event [86]. Sharma and colleagues demonstrated that patients who developed TdP with IVH were more likely to have a QT_B > 550 ms (85.7% vs 15.4%, OR = 33 [95% CI: 6, 135]) [55].

4.3.4. How does IVH compare with other antipsychotics in terms of risk?

One of the biggest unanswered questions pertains to the relative risk of IVH compared to other antipsychotics. Though common lore holds that IVH is associated with greater risk than most other agents, the literature is mixed. A recent large placebo-controlled study showed that ziprasidone caused significantly more QT prolongation than IVH [47]. As noted above, a 2010 study found increased risk with IVH compared with other agents but did not control for indication [52]. Patients requiring IVH (as opposed to an oral antipsychotics) may have been more commonly delirious with additional risk factors for QT prolongation, and more likely to be tachycardic due to agitation, leading to an overcorrection of QT via the use of Bazett formula. A 2011 study examined the World Health Organization (WHO) Individual Case Safety Report database and found that haloperidol was not associated with more frequent reporting of TdP than olanzapine or quetiapine [50]. There were 83 cases of TdP reported with IVH, 283 cases with other forms of haloperidol, 489 cases with olanzapine and 520 cases with quetiapine. There authors concluded that IVH carries no additional risk compared to other agents.

4.3.5. Summary of IVH and QT prolongation and TdP

The cumulative evidence suggests that the relationship between IVH, QT prolongation and TdP is not as strong as the level of oft-expressed concern would suggest. There is strong evidence from recent prospective studies that doses up to 20 mg daily do not appear to be associated with QT prolongation [55]. As of 2010, fewer than 100 instances of TdP had been reported, despite millions of patients having received the medication. To date, a thorough QT study has not been conducted with IVH to definitively demonstrate whether the QT prolongation is dose-dependent. No prospective head-to-head studies comparing IVH to other antipsychotics have been conducted, aside from one showing less QT prolongation with IVH compared to ziprasidone [47], and none have compared various forms of haloperidol.

5. Revised recommendations and rationale

Recommendations regarding the use of IVH with regards to the potential for QT prolongation and TdP were first issued in 1993 and have evolved since that time (Table 3). Despite recommendations in place, a 2012 study found that only 75% of patients receiving IVH had a baseline ECG and < 50% had a follow-up ECG within 24 h [51]. Our revised recommendations for the use of IVH are shown in Fig. 1. Given the increased risk for TdP in states of hypokalemia or hypomagnesemia, we recommend daily monitoring of magnesium and potassium for all patients receiving IVH, with daily repletion to 2 mEq/L and 4 mEq/L, respectively. With regard to ECG monitoring, despite all prior guidelines recommending a baseline ECG, the recent literature suggests that there is minimal if any QT prolongation with doses < 20 mg daily [24,25,29,33,34,45–48,53,89]. We therefore suggest that ECG monitoring of any sort may be unnecessary with low-dose IVH unless multiple other risk factors are present.

For doses exceeding 5 mg daily or for patients with 2 or more risk factors, we recommend a baseline ECG for all patients, when feasible. Risk factors include age > 65 years, female sex, cardiac disease, uncorrected electrolyte abnormalities and other QT-prolonging medications [59]. Because it may be challenging to estimate how much IVH will ultimately be required, obtaining a baseline ECG even if the dose is expected to be < 5 mg may be reasonable. In the event of a patient requiring medication for emergent danger of harm to self or others, a baseline ECG may not be possible. In this situation, a risk-benefit analysis should be completed, noting other risk factors for QT prolongation and the availability of rescue interventions should an episode of TdP occur. We also recommend that at least one follow-up ECG be checked, ideally within 30 min of administration, to capture the change at peak dose.

Our rationale in determining cut-off values for QT and IVH dose that should trigger additional monitoring is based on a belief that we should aim to minimize TdP while also recognizing that TdP is challenging to predict, that preventing it completely is probably not a reasonable goal, and that we must balance the risk of TdP with the very real and far more likely risks of an agitated patient causing harm to himself or others or continuing to experience distressing perceptual disturbances.

We would therefore recommend a daily ECG for patients receiving a total cumulative dose of > 25 mg daily. Two studies suggested that the largest changes in QT occurred with doses > 25 mg or > 35 mg, particularly when given over < 6 h [49,55,57]. In the 2010 systematic review, at least 39/52 (75.0%) and as many as 45/52 (86.5%) of patients with TdP who had documented cumulative doses received at least 25 mg of IVH [86].

The FDA has recommended telemetry at all times when using IVH. Our review of the literature and collective clinical experience, especially in light of the logistical hardship for some community settings, determines that this recommendation does not seem to be well-supported by the available literature and should be revisited. An alternative guide for clinicians would recommend continuous telemetry monitoring or alternative agents for those patients who demonstrate very high risk for TdP. While there is no clear literature to guide specific determinations, we would consider total cumulative doses of > 100 mg IVH or an accurately-corrected QTc of > 500 ms to be situations which may warrant consideration of telemetry. Sometimes, however, clinical exigencies require emergent use of IVH in a clinical location or situation where telemetry is not available, balancing clinical and patient/staff

Table 3
Prior recommendations regarding the use of IVH.

Article or guideline	Recommendations
Metzger & Friedman 1993 [21]	Baseline ECG with repeat at steady-state
	QTc > 450 ms or increase > 25% should prompt cardiology consultation and consideration of stopping haloperidol
DeSalvo 1995 [66]	QTc should be determined prior to treatment with IVH -If prolonged, great caution should be exercised
	Daily ECG throughout the duration of treatment
	Prolongation > 25% should prompt discontinuation
Lawrence 1997 [85]	Baseline ECG
	If baseline QTc > 440 ms, prescribe alternative treatment when possible
	If QTc increases by > 25%, discontinue haloperidol or reduce dose
	Electrolyte values evaluated at baseline and corrected
O'Brien 1999 [72]	Baseline ECG
	Hold IVH if QTc > 450 ms or increase by 15–20%
	Stop IVH if T waves flatten or U waves develop
	Electrolyte values evaluated at baseline and monitored periodically
FDA Warning 2007 [22]	Patients should receive continuous ECG monitoring (telemetry)
Meyer-Mazetti 2010 [86]	Screen for risk factors for QT prolongation and TdP
	Baseline ECG
	If significant risk factors exist or the baseline ECG reveals a prolonged QTc, patient should receive telemetry
	If cumulative doses of 2 mg are needed, the patient should be placed on telemetry

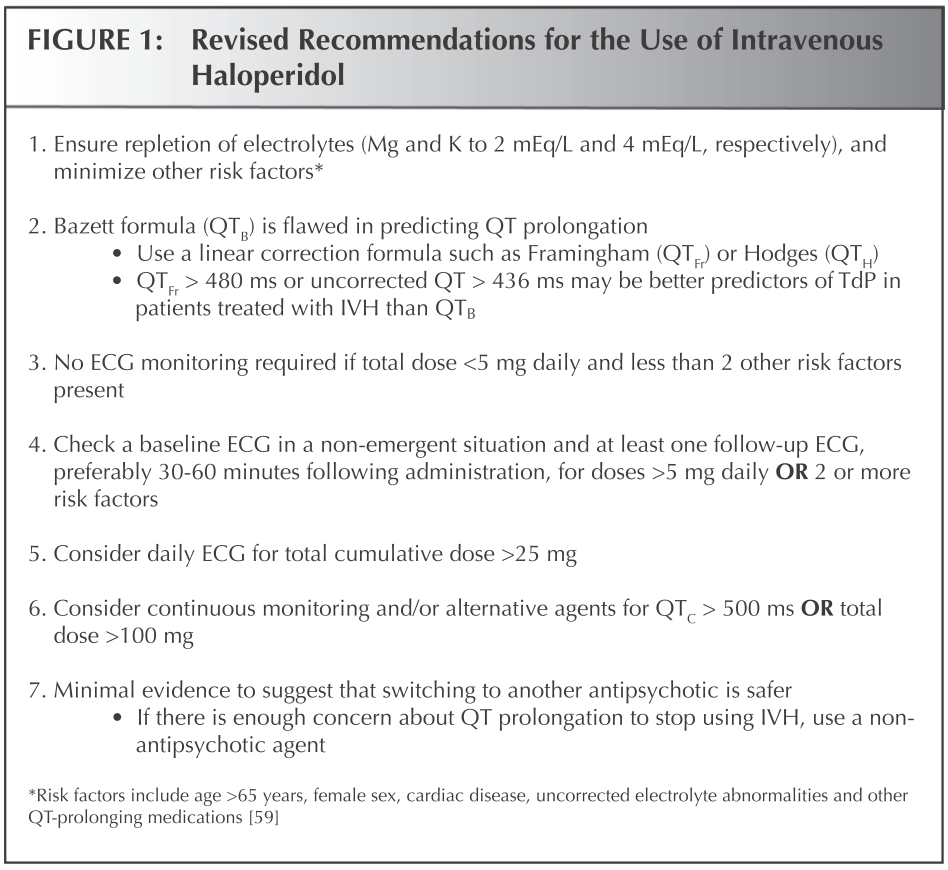

Fig. 1. Revised recommendations for the use of intravenous haloperidol.

safety considerations.

We would emphasize that there is very minimal evidence to suggest that switching from IVH to another antipsychotic agent is safer. Though many prior algorithms place IVH in a high-risk category along with ziprasidone and thioridazine and separated from other agents, this does not appear to be supported by the current evidence base. Only three studies have compared IVH to other antipsychotic agents, with two finding equal or decreased risk with IVH and the other suffering methodologic flaws [47,49,52]. Until better studies are conducted, it is not clear that the risk for QT prolongation and TdP is greater with IVH. Concurrently, aside from aripiprazole and possibly lurasidone, there are no antipsychotic agents that clearly separate out as being safer with regards to QT prolongation [81,82]. If practitioners are sufficiently concerned about QT prolongation or TdP so as to stop using IVH, a non-antipsychotic agent with no risk of QT prolongation, such as valproate or a benzodiazepine, would be alternative treatments. These come, however, with their own attendant risks in delirious patients.

Finally, it is imperative that an accurate QTc be derived through the use of a linear correction formula. The American Heart Association recommends always using a linear correction formula, and evidence comparing various correction formulas suggests that the use of a linear formula is more accurate and results in fewer medication restrictions [96,97]. We recommend using the Framingham formula (QT_{Fra} = QT + 0.154 (1 − RR)) or, for the purposes of deriving a faster estimate, the Hodges formula (QT_H = QT + 1.75 (HR-60)). Evidence suggests that a QT_{Fra} > 480 ms or an uncorrected QT > 436 ms may be a better predictor of TdP than QT_B in patients treated with IVH [56].

5.1. Limitations

Despite the systematic nature of this review, there are some limitations to our approach. There were a few articles that we could not obtain despite our efforts. While the abstracts and titles of these articles suggest less direct relevance, we cannot be certain that they would not have added additional important data. Another major limitation is incomplete information in many of the reports, particularly regarding correction of the QT interval for rate. Because every article relied on Bazett formula to correct, it is likely that many of the reported QTc intervals did not accurately capture the risk. Finally, the case report and case series literature introduces an element of selection bias, as cases are not reported unless they cause an exceptional outcome, like significant QT prolongation or TdP, meaning that such a literature tends to overestimate the risk.

6. Conclusions

Despite the widely accepted beliefs that IVH causes significant QT prolongation, TdP, and EPS, the evidence base suggests that the risk for these side-effects is low. Physicians, and particularly CL psychiatrists, should understand the limitations of the literature in accurately predicting the risk of bad outcomes with IVH. We recommend a revised risk algorithm, which does not rely on extensive ECG monitoring to mitigate the risk of TdP unless indicators of high risk are present, which may include multiple other risk factors, high doses of IVH, or significant QT prolongation.

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