Review Article

Propofol for Sedation for Direct Current Cardioversion

Abstract

Direct current cardioversion is a low-risk and standard procedure to restore normal sinus rhythm in patients with tachyarrhythmias. It requires sedation to facilitate the procedure, as it is painful and distressful. The preferred anesthetic drug must be short acting, producing conscious sedation, to enable rapid recovery after the procedure. In this sense, this narrative review focuses on the critical analysis of recent randomized studies and presents about the safety and effectiveness of propofol, comparing it with other established sedatives, mainly etomidate and midazolam. The research was performed on MEDLINE database with Propofol and Cardioversion keywords. In most cases, propofol comes to be the best option, with a quick recovery time and low rates of side effects. Different studies have demonstrated no inferiority when comparing to other drugs and, when these adverse events happened, they were easily and quickly handled. Exceptions in this scenario are those patients, particularly the elderly, with baseline important structural heart disease, in which etomidate with fentanyl has been pointed to lead to better hemodynamic stability.

Keywords: *Anesthesia, atrial fibrillation, cardioversion, etomidate, midazolam, propofol, sedation*

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Introduction

Direct current (DC) cardioversion is a painful and distressful procedure that requires short-term general anesthesia to promote patient comfort. All available anesthetic drugs have some limitations for DC cardioversion, and no current guideline specifies which anesthetic drug should be used. Therefore, the following three main drugs are most commonly used for this procedure: midazolam, etomidate, and propofol.

This narrative review focuses on the critical analysis of recent randomized studies to present an acknowledgment about the safety and effectiveness of propofol, comparing it with other established sedatives, for those who might perform DC cardioversion.

Methodology

Literature search for randomized studies was performed in the MEDLINE database. The PubMed search strategy included the following keywords: Propofol and Cardioversion. We also used the related articles' search strategy for each relevant article. We excluded studies with <20 patients from our review.

The main purpose of this review was to evaluate the safety and efficacy in propofol usage compared to etomidate and midazolam. Therefore, we searched, when possible, for side parameters such as decrease in blood pressure, cardioversion efficacy, apnea episodes, pain on injection, recall, myoclonus, nausea, vomiting, and satisfaction with the procedure.

Direct Current Cardioversion

External electrical cardioversion is a low-risk and standard procedure that uses DC to restore normal sinus rhythm in patients with tachyarrhythmias. It was first stated in the 1960s[1] and is, until nowadays, widely performed to convert supraventricular and ventricular tachyarrhythmias into a normal sinus rhythm.[2] Anesthetic drugs are required most often for elective DC cardioversions; however, they may be necessary an emergency cardioversion if the arrhythmia is dangerously compromising the patient hemodynamic. It is a procedure used in the treatment of atrial fibrillation and flutter, alternatively or in addition to pharmacological therapy, with high conversion rate.[2-5]

A rapid onset and offset of anesthetic action, quickly inducing analgesia and loss of consciousness, and also a short elimination

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half-time, is desirable for a DC cardioversion. Besides, it should cause the minimum cardiovascular and respiratory side effects, such as negative inotropic effect for heart failure patients, and should not cause vomiting and nausea or accumulate if additional doses are necessary.[1,2,6] In this sense, medications such as thiopentone, methohexital, diazepam, and inhaled anesthetic agents, such as isoflurane and sevoflurane, have already been used. However, none of these drugs could achieve all those qualities.[1,3,4] Currently, the most used agents are propofol, etomidate, and midazolam due to their favorable pharmacokinetics and adverse effect profile. In hospitals in the United Kingdom, 90% of DC cardioversions are performed with propofol, followed by etomidate in 7%.[3]

Propofol Pharmacokinetics

Propofol is an alkylphenol that derives from 2,6-diisopropylphenol. It is administrated in emulsion that appears as a whitish opaque liquid due to the light dispersion caused by the very small droplets of fat. Propofol has the concentration of 1% or 2%, depending on the country.[7,8] This substance can sedate by doing a positive modulation on the inhibitory function of $GABA_A$ receptors.[7]

Its favorable pharmacokinetics is the main reason why it is, in many countries, the most common intravenous nonopioid anesthetic drug used for induction of anesthesia.[8] It is rapidly distributed and the duration of action ranges from 3 to 8 min, an interesting profile for procedures that require short-term general anesthesia like DC cardioversion. Propofol is mainly metabolized by the liver, but almost 30% of bolus dose is metabolized by extrahepatic metabolism, especially the lungs, giving it a high plasma clearance which is the reason for better recovery; after that, the metabolites have renal excretion, with a quick clinical recovery, despite its accumulation in the adipose tissue[7,8] [Table 1].

Propofol causes vasodilatations in both venous and arterial circulations, leading to the most relevant reduction of systemic blood pressure among all intravenous anesthetics.[3] Another possible effect is a negative inotropic effect.[6]

The hypotensive effects are more likely to occur in elderly individuals with baseline structural heart disease. It can also lead to respiratory depression and apnea; likewise, it reduces the response to hypoxia and hypercapnia. However, by reducing upper airway reflexes, it gives a better intubation condition without the use of neuromuscular blocking agent.[7,8,10] It also has a desirable antiemetic activity.

Table 1: Pharmacokinetic profile of propofol

Propofol	Pharmacokinetic
Onset of action	20-40 s[9]
Duration time	5-10 min[9]
Half-time elimination	4-23 h[7]
Clearance	20-30 mL/kg/min[7]
Dosage	1-2.5 mg/kg IV[7]
Metabolism	Liver[7]

IV: Intravenous

Propofol for Direct Current Cardioversion

Among randomized studies,[11-26] the outcomes investigated are heterogeneous. Furthermore, the doses and also the professional leading the anesthesia were different in many cases, which could have influenced their results [Table 2].

The main parameters that we sought to evaluate were the safety and efficacy in propofol usage compared to etomidate and midazolam. To evaluate safety, we took into account parameters such as blood pressure and the occurrence of respiratory events. To evaluate efficacy, we considered the time of sedation and recovery, as well as reports of pain during the procedure. Other side effects such as nausea and myoclonus were also considered.

Propofol can promote hypotension as it causes arterial and venous vasodilatation, which may result in a significant decrease in blood pressure. Systolic and diastolic blood pressures were lower with propofol compared to etomidate in three out of seven studies.[17,18,22] However, none reported severe reductions in blood pressure that could lead to shock, and the rare cases of hypotension were all easily controlled. It must be noted that most of the studies included only American Society of Anesthesiologists class I and II patients or excluded those with low left ventricle ejection fractions.[17,23,26]

Some studies compared added fentanyl, an opioid analgesic, to propofol and etomidate. The concomitant use of propofol and fentanyl caused greater reductions in blood pressure, while it showed to be beneficial with etomidate.[15-18] When compared with midazolam, one study showed that the decrease in systolic blood pressure was more pronounced with propofol,[19] while others did not report difference.[10,13,14,20] It must be highlighted that even in studies that presented statistically significant reduction in blood pressures, no relevant clinical effect was found. In addition, elderly patients with structural heart diseases showed to be more prone to hypotension, especially when fentanyl was administrated along with propofol.[15,16]

The majority of studies considered respiratory depression, apnea, need for intubation, or manual ventilation as respiratory events. They showed that all these drugs are equally safe, except for a study,[14] in which more patients in the propofol group had apnea and needed artificial ventilation (15/20 vs. 6/20; $P < 0.05$). Some of these cases required manual ventilation followed by a quick recovery, and no intubation was necessary. In opposition, when fentanyl is added to propofol and etomidate, the occurrence of obstruction of the upper airway occurred two times more

Table 2: Randomized clinical studies with propofol for direct current cardioversion

Study	Study design	Population	Intervention	Target	Oxygen supplementation and monitoring modalities	Results
Propofol versus etomidate						
Hullander *et al*., 1993[24]	RCT Parallel design	40 patients Elective Hospital setting	Propofol (50 mg/min) Etomidate (8 mg/min) Both with lidocaine 2.5% (0.5 mg/kg)	Loss of response to verbal stimulus	Oxygen (2 L/min) via nasal canula NIBP	Hypotension: No definition of hypotension given. Absolute BP values not presented Apnea: 10% versus 5% (PNE) Recall: Both 0% Nausea: Both 0% Pain at injection site: Both 0% Myoclonus: 0% versus 45% (PNE) Successful cardioversion: 80% versus 85% (PNE)
Kick *et al*., 1996[14]	RCT Parallel design	40 patients (ASA II/III) Elective Hospital setting	Propofol (1.5 mg/kg) Etomidate (0.25 mg/kg)	Loss of eyelid reflex	40% oxygen via face mask NIBP	Hypotension: Both had significant fall in BP (measured by NIBP) Apnea: 75% versus 30% (P<0.05) Pain at injection site: 5% versus 25% (P<0.05) Myoclonus: 0% versus 60% (PNE) Successful cardioversion: Both 70% Number of shocks: 37 versus 40 (PNE)
Munoz Martinez *et al*., 2002[22]	RCT Parallel design Nonblinded	50 patients (ASA status not given) Elective Persistent AF or flutter Procedure room, CCU Monophasic defibrillators	Propofol (1 mg/kg IV over 1 min) Etomidate (0.15 mg/kg + midazolam 1 mg IV over 1 min)	Loss of response to verbal or tactile stimulus	50% oxygen via face mask	Hypotension: More evidenced with propofol (P=0.02) Apnea: 12% versus 16% (NS) Recall: 0% versus 4% (NS) Myoclonus: 0% versus 20% (PNE) Pain at injection site: 8% versus 0% (PNE) Number of shocks: Both 2 Success of cardioversion: Both 72% (NS) Time to recovery: 518 s versus 651 s (P=0.01) Time to sedation: 95s (±33) versus 89 s (±30) (NS)

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Table 2: Contd...

Study	Study design	Population	Intervention	Target	Oxygen supplementation and monitoring modalities	Results
Akcaboy *et al*., 2007[18]	RCT Parallel design	40 patients (ASA II/III) Elective Persistent AF, flutter, SVT Hospital setting	Propofol (0.5 mg/kg IV over 15 s) Etomidate (0.1 mg/kg IV over 15 s) Both with remifentanil (0.75 µg/kg IV over 90 s)	OAA/S score of 2	Oxygen (2 L/min) via face mask NIBP Digital pulse oximeter	Hypotension: More evidenced with Propofol (P<0.001) Apnea: 10% versus 0% (P=0.003) Recall: 5% versus 0% (PNE) Nausea/vomiting: 10% versus 15% (PNE) Pain at injection site: 15% versus 0% (PNE) Myoclonus: Both 0% Patient satisfaction: Good 10% versus 15%; excellent 90% versus 85% (PNE) Number of shocks: 26 versus 28 (PNE) Time to recovery: 11.2 m (±0.74) versus 13.4 (±1.03) (P<0.001) Time to sedation: 2.93 m (±0.25) versus 3.3 (±0.22) (P<0.001)
Desai *et al*., 2015[15]	RCT Parallel design Single blind	60 patients (ASA I/II/III) Persistent AF, SVT stable monomorphic TV Hospital setting	Propofol (1 mg/kg + 0.5 mg/kg) Etomidate (0.1 mg/kg + 0.05 mg/kg) Both with lignocaine ! min before propofol or etomidate (0.5 mg/kg) and fentanyl (1 µg/kg)	No response to verbal commands and loss of eyelid reflex	Oxygen via face mask NIBP ECG Digital pulse oximeter	Hypotension: 33% versus 17% (P=0.23) Respiratory depression: 20% versus 0% (P=0.02) Nausea/vomiting: 0% versus 3% (PNE) Myoclonus: 0% versus 27% (P=0.004) Pain at injection site: Both 0% Success rate: 80% versus 83% (PNE) Number of shocks: 2.1±1.3 versus 1.9±0.9 (P=0.49) Time to recovery: 11±3 min versus 7±2 min (P<0.001)
Siedy *et al*., 2010[17]	RCT	100 patients (ASA II/III/IV) Elective NYHA I/II/III CCU Monophasic defibrillator	Propofol (1 mg/kg) Etomidate (0.15 mg/kg + fentanyl 1 µg/kg)	Inability to open the eyes when commanded and a lack of eyelid reflex	Oxygen supplementation only if apnea >30 s or oxygen saturation <90% NIBP Digital pulse oximeter	Hypotension: Values of BP were lower in propofol group (P<0.05) Apnea: 6% versus 4% (NS) Nausea: 2% versus 14% (P<0.05) Vomiting: 0% versus 8% (P<0.05)

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Table 2: Contd...

Study	Study design	Population	Intervention	Target	Oxygen supplementation and monitoring modalities	Results
						Pain at injection site: 8% versus 22% (P<0.05) Myoclonus: 10% versus 28% (P<0.05) Time to recovery: 4.7±2.2 min versus 6.7±4.9 min (P<0.01)
Kalogridaki *et al*., 2011[16]	RCT Parallel design	46 patients (ASA II/III/IV) Elective Persistent AF Electrophysiology laboratory Biphasic defibrillator	Propofol (0.5 mg/kg IV over 30 s) Etomidate (0.1 mg/g IV over 30 s) Both with fentanyl (50 µg)	No response to verbal commands and loss of eyelid reflex	100% oxygen via a facemask NIBP ECG Digital pulse oximeter	Hypotension (decrease in SBP ≥20%): 20% versus 0% (P=0.05) Apnea: 28% versus 48% (P=0.22) Recall: 12% versus 5% (P=0.61) Pain at injection site: 28% versus 19% (P=0.51) Myoclonus: 0% versus 52% (P=0.0004) Successful cardioversion: 95% versus 81% (PNE) Number of shocks: 29 versus 23 (P=0.85) Time to recovery: 269 s±112 versus 251±167 (P=0.67)
Propofol versus midazolam						
Parlak *et al*., 2006[23]	RCT Double blinded Parallel design	74 patients (ASA status not given) Elective and emergency Persistent AF Emergency department and CCU Monophasic defibrillator	<65 years. Midazolam (2 mg) Then 1 mg of midazolam every 2 min <65 years. Propofol (20 mg). Then 20 mg propofol every 2 min ≥65 years. Midazolam (2 mg) Then 1 mg of midazolam every 2 min ≥65 years. Propofol (20 mg). Then 20 mg propofol every 2 min All with fentanyl: <65 years: 1 µg/kg/≥65 years: 0.5 µg/kg	RSS 5	Oxygen (4 L/min) NIBP Digital pulse oximeter	Desaturation: 2/12 versus 1/11 versus 15/25 versus 4/22 (P=0.001) Apnea: 1/12 versus 1/11 versus 6/25 versus 2/22 (P=0.39) Recall: 0/12 versus 1/11 versus 4/25 versus 1/22 (PNE) Patient satisfaction: Satisfied: Satisfied 12/12 versus 11/11 versus 23/25 versus 20/22 (PNE) Unsure if satisfied: 0/12 versus 0/11 versus 2/25 versus 2/22 (PNE)

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Table 2: Contd...

Study	Study design	Population	Intervention	Target	Oxygen supplementation and monitoring modalities	Results
Guerra *et al*., 2014[19]	RCT Parallel design Open-blinded	204 patients (ASA status not given) Elective Persistent AF Hospital setting Biphasic defibrillator	Propofol (1 mg/kg + 0.5 mg/kg every 3 min) Midazolam (3 mg + 2 mg every 2 min + flumazenil 1 mg)	RSS 4 or 5	100% oxygen via a facemask NIBP ECG Digital pulse oximeter	Decrease in SBP: More important with propofol (P=0.002) Clinical hypotension: Both 0% Bradycardia: 9% versus 6% (P=0.43) Respiratory depression: Both 4% (P=1) Recall: Both 3% Time to full recovery: 14±6 min versus 14±7 min (NS) AF recurrence (24 h): 27% versus 18% (NS) Length of hospitalization: 31 h versus 28 h (P=0.003)
Propofol versus thiopentone						
Sternlo and Hägerdal, 1991[25]	RCT Parallel design	44 patients (ASA status not given) Elective Persistent AF	Propofol Thiopentone	Loss of eyelid reflex	100% oxygen via a facemask NIBP ECG	Apnea: 8.7% versus 9.5% (PNE) Pain at injection site: 4% versus 0% (PNE) Bradycardia: Both 0% Successful cardioversion: 87% versus 90% (PNE) Mean time to recovery: 9 min versus 5.8 min (P<0.002)
Propofol versus sevoflurane						
Karthikeyan *et al*., 2002[26]	RCT Parallel design	61 patients (ASA I/II/III) Elective Persistent AF or flutter Hospital setting	Propofol (6 µg/mL target controlled infusion) Sevoflurane 8% (inhaled in 50% oxygen/nitrous oxide) Both with nitrous oxide and glycopyrronium	Loss of eyelash reflex	50% oxygen via a facemask NIBP Digital pulse oximeter	Hypotension: Propofol group had lower BPs in the recovery room (P<0.001) Mean time to recovery: 738 s (±355) versus 318 s (±127) (P<0.001) Apnea: 26% versus 17% (PNE) Nausea/vomiting: 3% versus 7% (PNE) Pain at injection site: 13% versus 0% (PNE) Myoclonus: 19% versus 10% (PNE)

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Table 2: Contd...

Study	Study design	Population	Intervention	Target	Oxygen supplementation and monitoring modalities	Results
						Satisfaction: pleasant 35 versus 33%; indifferent 42 versus 34%; unpleasant both 3% (PNE) Successful cardioversion: 93% versus 83% (PNE)

RCT: Randomized controlled trial, BP: Blood pressure, PNE: *P* value not established by the authors, AF: Atrial fibrillation, SVT: Supraventricular tachycardia, VT: Ventricular tachycardia, ASA: American Society of Anesthesiologists physical status classification, NYHA: New York Heart Association functional classification, RSS: Ramsey Sedation Scale, OAA/S: Observer Assessment of Alertness/Sedation, ECG: Electrocardiography, NIBP: Noninvasive BP, NS: Not significant, IV: Intravenous, SBP: Systolic BP, CCU: Coronary care unit, TV: Ventricular tachycardia

in the etomidate plus fentanyl group than in the propofol plus fentanyl group (P = 0.22), events that were quickly solved with jaw thrust and chin lift[16] [Figure 1].

Since cardioversion DC is a very brief procedure, it is interesting a short duration of sedation. Comparing the time of sedation, propofol had the shortest time, followed by etomidate. Midazolam, as expected, has the longest sedation time, and that explains its common use along with its antagonist flumazenil in such a way that the median sedation time sharply decreases. Even though it shortens the sedation time, it increases resedation rate, which is explained by the fact that flumazenil has a much shorter half-life in comparison to midazolam and can be dangerous if it occurs when the patient is no longer being monitored.[12,13,19]

In order to evaluate the efficiency, we also considered the recovery time. Despite its subjective characteristic, some studies used known scores such as Aldrete, Ramsay, and Steward, while others did some other tests including the level of sedation, memory, comprehension, and collaboration, among others. These results were similar to those regarding the sedation time. Propofol showed to be superior to others, with a quick and better recovery. The usage of etomidate is also a good choice when recovery time needs to be short; it takes just a little longer than propofol. Midazolam, on the other hand, if not followed by flumazenil, can reach a recovery time of up to 60 min.[13] Patients that recalled pain during the procedure were present in almost all of the studies, but with no significant difference between the groups [Figure 2].

In all of the studies, side effect criteria included pain during the injection, nausea, vomiting, and myoclonus. Etomidate presented the worst profile. The findings of pain during the injection were not consistent, but two of them reported that etomidate group had more cases of pain during the injection.[10,14,17] Some studies used intravenous lignocaine prophylactically [Figure 3]. Propofol has anti-emetic properties that contribute to its favorable side effect profile, while etomidate showed the highest rates of nausea and vomiting.[17] Besides that, etomidate causes a much higher incidence of myoclonus, which can reach up to 80% of the nonpremedicated patients,[15,21] with important interference in the electrocardiographic (ECG) signals. The incidence of myoclonus with etomidate is of 45%[24] and,

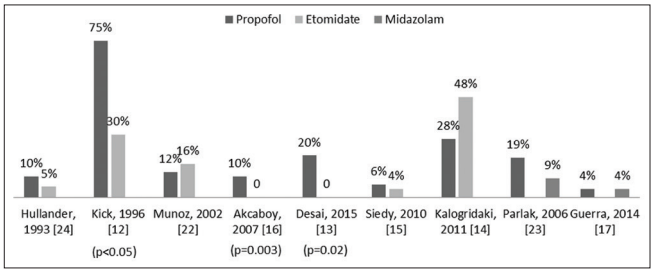

Figure 1: The occurrence of respiratory depression among studies

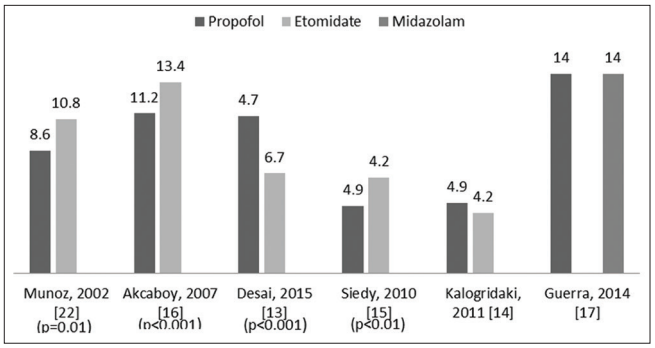

Figure 2: A comparison of the time to recovery from anesthesia among studies

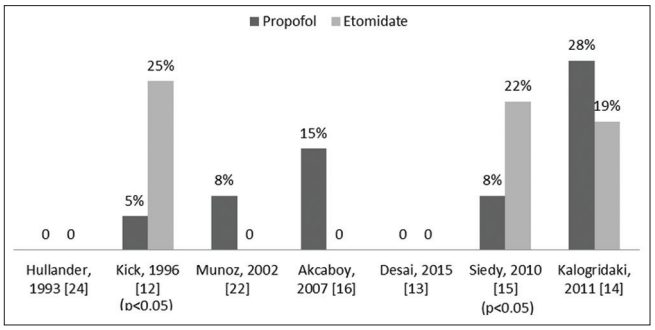

Figure 3: The occurrence of pain at the injection site among studies

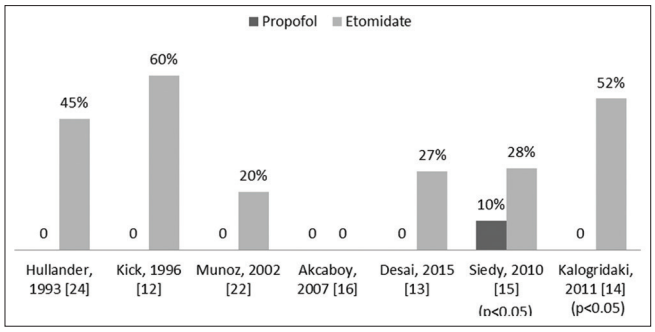

Figure 4: The occurrence of myoclonus among studies

when fentanyl is added, the rate of this complication falls to 28%[17] [Figure 4].

Discussion

There are some points that deserve to be highlighted regarding the three main drugs used in DC cardioversion procedures. Midazolam is an effective anesthetic, encompassing hemodynamic stability along with a great side effect profile. Its main limitation is the increased recovery time in comparison with the other drugs, resulting in the necessity of a compulsory use of flumazenil. Compared to midazolam, etomidate presents to be a better option for most cases. Its recovery time is dramatically shorter, whereas the hemodynamic stability remains safe. Etomidate's disadvantage is its side effect profile, especially myoclonus that can interfere with the ECG interpretation. In most cases, propofol comes to be the best option. It has a quick recovery time and low rates of side effects. According to drug's mechanisms, hypotension and respiratory depression could be expected in several cases; however, different studies have demonstrated no inferiority when comparing to other drugs and, when these adverse events happened, they were easily and quickly handled. Exceptions in this scenario are those patients, particularly the elderly, with baseline important structural heart disease, in which etomidate with fentanyl has been pointed to lead better hemodynamic stability.

Review limitations

The main limitation of this review is the limited number of randomized trials investigating the best anesthetic drug for elective DC cardioversion. Furthermore, the studies encountered are heterogeneous, had a small sample size, investigated different outcomes, used different drug doses, and had different professionals leading the anesthesia. A future large randomized clinical trial comparing directly propofol with other most administrated drugs, such as etomidate and midazolam, would be interesting to establish the exact role of each sedative. Until then, the current choice must be individualized based on the clinical aspects of the patient and on the information obtained from the limited studies available.

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Conflicts of interest

There are no conflicts of interest.

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