Alpha-2 Agonist Discontinuation Syndrome: Systematic Review of Epidemiology, Clinical Presentation and Treatment

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Background

- Alpha-2 agonists have gained popularity for a wide range of indications in the recent years (e.g. sedation, opioid withdrawal)
- A key concern of clinicians is the development of adverse effects following abrupt discontinuation (e.g. hypertensive crisis)
- Existing reviews lack comprehensive, systematic clinical question-based development and reporting process

Objective

- To utilize a novel multi-tiered approach for conducting a comprehensive systematic review to characterize the alpha-2 agonist (i.e. clonidine, dexmedetomidine) discontinuation syndrome in terms of:
  - Incidence, onset, risk factors and clinical presentation
  - Efficacy and safety of therapeutic options

Methods

- Search: Electronic databases (CENTRAL, Embase, MEDLINE) and grey literature (clinical trial registries, conference)
- Inclusion: Studies of any design of patients ≥1 month old that assessed any of the characteristics within our objectives
- Study quality: Assessed using the following validated tools:
  - Naranjo scale (case reports/series): Determines the likelihood that the adverse effect is caused by the medication based on an assigned score
  - Newcastle-Ottawa Scale (cohort/case-control/cross-sectional studies) and Cochrane Risk of Bias Tool (randomized controlled trials): Evaluates key domains at risk of bias
- Bradford Hill criteria: Applied to overall evidence to determine causality between alpha-2 agonist discontinuation and the described discontinuation syndrome

Results

Table 1. Study and patient characteristics

Study design – no. (%)	**All studies (N=100)**
Case reports/series	98 (98%)
Cohort studies	1 (1%)
Randomized controlled trials	1 (1%)
Patient characteristics	**All patients (n=1294)**
Age – median (range)	49 (0.15-86)
Pediatric patients – no. (%)	213 (17%)
Alpha-2 agonist used and indication of use prior to withdrawal- no. (%)	
Clonidine	577 (45%)
Dexmedetomidine	717 (55%)
Hypertension	486 (38%)
ICU sedation	784 (61%)

Results

Figure 1. Incidence of discontinuation syndrome and sub-syndromes

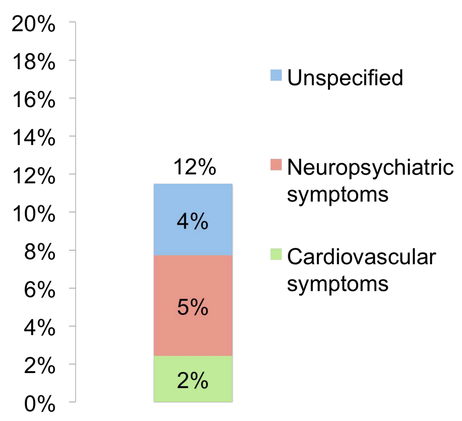

Figure 2. Incidence of the syndrome in patients who abruptly discontinued vs those who tapered

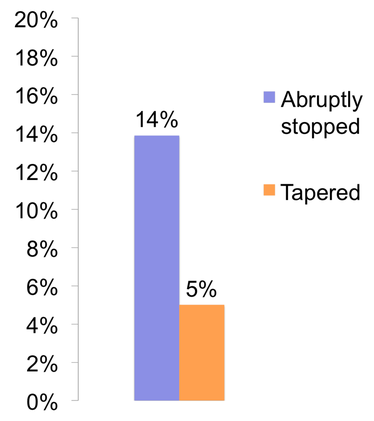

Figure 3. Proportion of patients receiving each class of agents

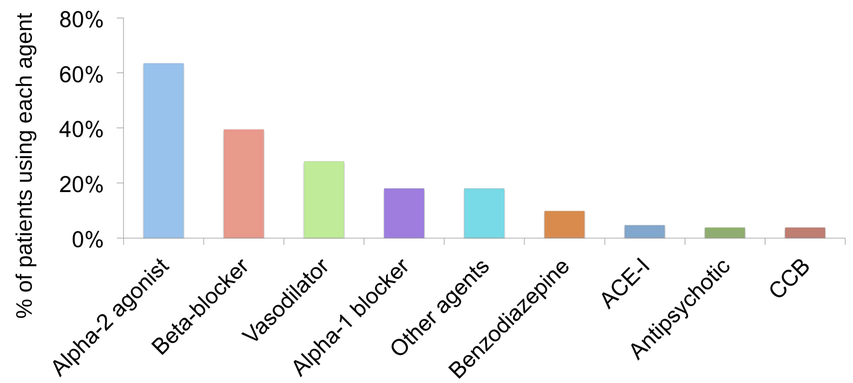

Table 2. Treatment outcomes	**All patients treated (n=233)**
No. of drugs received – median (range)	2 (1-7)
Patients requiring ≥3 drugs sequentially to achieve control	19 (8%)
Mortality	0 (0%)
Serious adverse event	4 (2%)
Total adverse drug reaction	10 (4%)
BP control within 24 hours	63 (76%)
HR control within 24 hours	24 (29%)
Resolution of neuropsychiatric symptoms within 24 hours	75 (79%)

Results

Table 3. Causality assessment using the Bradford Hill criteria (N=100)

Type of evidence	Criteria	Assessment
Direct	**Strength**	No studies with RR/OR/HR
	Temporality	Exposure preceded outcomes in 88% of cases
	Experiment	As described in studies herein
Mechanistic	**Biological Gradient**	2/3 and 1/2 of studies correlated syndrome with dose and duration of use, respectively
	Biological plausibility	Increase in plasma catecholamine levels after alpha-2 agonist withdrawal
Parallel	**Consistency**	≥2 studies associated overall withdrawal syndrome and neuropsychiatric/CV symptoms with agent discontinuation
	Specificity	Multiple studies reported the same set of symptoms
	Coherence	All components of the syndrome are caused by acute precipitants
	Analogy	Discontinuation syndrome also associated with withdrawal of other drugs

Limitations

To our review

- Required post-hoc revisions to protocol (due to the use of a novel review approach where no guidelines for design and reporting exist)
  - Ensured that changes and their impact to results were transparent

To the included literature

- Many trials from 1970-1990's → differing standards of care

Conclusion

- Discontinuation syndrome following alpha-2 agonist withdrawal:
  - Is a relatively common occurrence
  - May appear up to 17 days after discontinuation
  - Still occurs following tapered withdrawal
- Reasonable treatment options include reinitiating alpha-2 agonist at pre-discontinuation dose, as well as usual treatment regimens for hypertensive crisis

Abbreviations used: CCB = calcium channel blocker; ACE-I = ACE inhibitor; BP = blood pressure; HR = heart rate; CV = cardiovascular