

Appendix 2

Search strategy and method for case report analysis

Objective	To identify pharmacological treatments to control arterial hypertension in the setting of serotonin syndrome.
Eligibility criteria	<p>Trials, observational studies or case reports in which participants fulfil the following criteria:</p> <p>Inclusion criteria: Patients (of any age) fulfilling one or more of the current three diagnostic criteria for serotonin syndrome (Sternbach, Radomski or Hunter).</p> <p>Exclusion criteria: We excluded all cases</p> <p>(1) not meeting any of the diagnostic criteria despite claiming a diagnosis of serotonin syndrome,</p> <p>(2) being etiologically uncertain despite meeting the diagnostic criteria,</p> <p>(3) containing insufficient clinical information to rate,</p> <p>(4) being historical, or</p> <p>(5) implicating first-generation antipsychotics or concomitant Neuroleptic Malignant Syndrome (NMS).</p>
Information sources	<ol style="list-style-type: none">1. MEDLINE(R)2. ISI Web of Science: Science Citation Index Expanded3. Cochrane Central Register of Controlled Trials CENTRAL, The Cochrane Library4. CINAHL5. TOXNET Toxline search6. Clinicaltrials.gov (www.clinicaltrials.gov)
Search	<p>Search was performed with the terms ["serotonin syndrome" OR "serotonin toxicity"] AND ["hypertension" OR "hypertensive"]</p> <p>Limits for case reports: From 2004, by which time Hunter criteria had been published and all three diagnostic criteria become available, until 31 December 2016.</p>
Study selection	Inclusion and exclusion criteria as above.
Data collection process	<p>Systematic review: We identified no studies meeting the inclusion criteria.</p> <p>Case report analysis: We abstracted all eligible cases into a new dataset, including general patient characteristics, onset, clinical course, mode of presentation, symptoms, diagnostic criteria, associated medications, treatment and outcome. Two investigators (UW and FJ or UW and MO) independently double-rated all cases regarding Hunter (HC), Sternbach (SC) or Radomski (RC) criteria. If the article fulfilled the inclusion criteria, two authors then reviewed the full text of each article to extract data on medication, clinical data, treatment and outcome. Disagreements between authors' ratings were resolved by consensus.</p>
Data items	Symptoms of serotonin syndrome: 20 symptoms appearing in any of the three diagnostic criteria sets.

	<p>Blood pressure (BP) at presentation and highest / lowest BP reported. Pharmacologic treatment of arterial hypertension (substance) and time to normalisation. Death.</p>
Bias	<p>As there were no trials or observational studies available we relied on case reports only. At publication level: publication bias favouring unexpected or uncommon cases. As arterial hypertension is no criterion in Sternbach and Hunter classification, arterial hypertension may be underreported. At study level: two investigators (UW and FJ or UW and MO) independently double-rated all cases regarding HC, SC and RC, and reported BP.</p>
Summary measures	Time to normalization of BP after given treatment
Synthesis of results	Descriptive