SYSTEMATIC REVIEW PROTOCOL FOR ANIMAL INTERVENTION STUDIES

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VERSION 1.0 (JULY 2014)

Item #	Section/ item	Description	Check for approval
	General		
1.	Title of the review	The effects of ibogaine on drug use in the animal model of addiction, a systematic review and meta-analysis.	
2.	Authors (names, affiliations, contributions)	Maarten Belgers [2]; performing research, in- and exclusion, data extraction, quality assessment, data-analyse, writing paper Marlies Leenaars [1]; in- and exclusion, data extraction, quality assessment, data-analyse, writing paper Merel Ritskes-Hoitinga [1]; designing research, writing paper Arnt Schellekens [2]; performing research, writing paper Carlijn R Hooijmans [1]; in- and exclusion consultancy, designing and supervising research, writing paper. Departments of [1]SYstematic Review Centre for Laboratory animal Experimentation (SYRCLE) [2] Psychiatry, [3] Medical Library, Radboudumc, Nijmegen, The Netherlands.	
3.	Other contributors (names, affiliations, contributions)	Alice Tillema [3], search strategy design	
4.	Contact person + e-mail address	Maarten Belgers; Maarten.Belgers@radboudumc.nl	
5.	Date of protocol registration	29-09-2014 (update 16-12-2014)	
	Background		
6.	What is already known about this disease/ model/ intervention? Why is it important to do this review?	The global burden of disease is substantially attributable to substance use disorders (SUD). Addiction is a chronic disease and although we have successful treatment programs to detoxify patients with SUD, there is currently only limited evidence based treatment for preventing relapse among abstinent patients exist. A major cause for relapse is craving; the intense longing to use a drug. This has led to a search for alternative treatment modalities, with some more promising than others. For example ibogaine, a naturally occurring substance in an African shrub, has been claimed to reduce relapse in dependent patients. Indeed, case reports mention relieve of withdrawal symptoms and reduction of relapse during and after detoxification in humans, mainly in the context of an opioid addiction. Even though ibogaine has increasingly been used for this purpose the last decades, mostly in a lay-scene, there are no human clinical trials about the safety and efficacy of ibogaine in patients with SUD. However a large body of animal studies suggests ibogaine could have therapeutic potential. Animal studies demonstrated that ibogaine, even after a single dose, are	

		effective in validated models of the major components of the addiction cycle. Studies about the neurobiological working mechanism of ibogaine showed effects on key factors within current hypotheses about addiction. A major concern in the use of ibogaine is its potential cerebellar and cardiac toxicity, which has been described in animal studies as well as human case reports of fatalities. Since numerous animal studies have been published over the last few decades, systematic reviews and analysis of the results is urgently needed in order to guide experimental studies.	
	Objectives of this SR		
7.	Specify the disease / health problem of interest	Substance Use Disorder	
8.	Specify the population /species studied	All species	
9.	Specify the intervention/exposure	Ibogaine given to the animal in vivo	
10.	Specify the control population	No ibogaine treatment (placebo or sham or no intervention)	
11.	Specify the outcome measures	1) Behavioural outcome measures: a. Self administration of drugs in an animal addiction model of self administration b. Drug induced place preference learning and displaying in animal addiction model of conditioned place preference 2) Neurobiological outcome measures: change in dopamine and/or serotonin brain tissue levels of a chronic drug using animal. 3) Toxicological outcome measures: a. Purkinje cell loss in cerebellum b. Cerebellar cell loss as measured with GFAP staining c. Observed motor impairment d. Effect on heart rhythm	
12.	State your research question (based on points 7-11)	1 Does ibogaine reduce drug use in animal models of chronic addiction and is this effect sustainable? ? 2 What are the neurobiological effects of ibogaine administration on important neurotransmitter systems in the brain of an addicted animal ? 3 What are the toxic effects of ibogaine on motor functioning, cerebellar cell structure and cardiac rhythm?	
	Methods:		
	Search and study identification		
13.	Identify literature databases to search (*e.g.* Pubmed, Embase, Web of science)	X MEDLINE via PubMed X Web of Science ☐ SCOPUS X EMBASE X Other, namely: Cinahl, Psycinfo ☐ Specific journal(s), namely:	
14.	Define electronic search strategies (*e.g.* use the step by step search guide	See *supplementary file 1 search strategy*	

	[1] and animal search filters [2, 3])		
15.	Identify other sources for study identification	XReference lists of included studies ☐Books XReference lists of relevant reviews ☐Conference proceedings, namely: ☐Contacting authors/ organisations, namely: ☐Other, namely:	
16.	Define search strategy for these other sources	Screening the reference lists for relevant titles and screening the abstracts of these relevant titles	
	Study selection phases		
17.	Define screening phases (*e.g.* pre-screening based on title/abstract, full text screening, both)	First phase screening by title and abstract, second phase screening by full text of the eligible articles	
18.	Specify number of reviewers per screening phase	First and second phase: 2 reviewers. In case of differences of opinion, it will be solved through discussion or by consulting a third investigator	
	Study selection criteria. Define all inclusion and exclusion criteria based on:		
19.	Type of study (design)	Inclusion criteria: all animal intervention studies about ibogaine treatment versus no ibogaine treatment on the effect of it in animal models of addiction, plus all animal intervention studies about the toxicity of ibogaine, plus all animal interventions studies about neurobiological effects in animals with chronic drug use. Exclusion criteria: not a primary study, reviews	
20.	Type of animals/ population (*e.g.* age, gender, disease model)	Inclusion criteria: all animal species Exclusion criteria: human studies	
21.	Type of intervention (*e.g.* dosage, timing, frequency)	For research question 1 and 2: Inclusion criteria: studies where ibogaine is administered to animals in vivo within the context of an addiction model Exclusion criteria: no ibogaine administered, ibogaine administered to healthy (non addicted) animals, ibogaine administered in vitro, no addiction model, ibogaine contamination/combination therapy, no control group For research question 3: Inclusion criteria: studies where ibogaine is administered to animals in vivo Exclusion criteria: no ibogaine administered, ibogaine administered in vitro, ibogaine contamination /combination therapy, no control group	
22.	Outcome measures	Inclusion criteria: Behaviour: self-administration , place preference Neurobiology: Dopamine and serotonin brain levels. Toxicology: Purkinje cell loss, motor impairment, cardiac rhythm Exclusion criteria: other outcome measures like withdrawal (including tail flick and hotplate test),	

		locomotor activity, antinociception, pluz maze test, serotonin syndrome, lethality and blood pressure, etc.	
23.	Language restrictions	Inclusion criteria: all languages Exclusion criteria: none	
24.	Publication date restrictions	Inclusion criteria: all publication dates Exclusion criteria: none	
25.	Other	Inclusion criteria: none Exclusion criteria: none	
26.	Sort and prioritize your in- and exclusion criteria per selection phase	Phase one and two, exclusion: 1. Duplicate 2. Review 3. Not an original study 4. Human study 5. Not an in vivo animal study 6. No ibogaine administration 7. No control group 8. Contamination/combination therapy 9. Study does not contain a research question in the field of addiction, neurobiology or toxicology Phase three, inclusion: 1. Study is about animal model of self-administration 2. Study is about animal model of conditioned place preference/aversion 3. Study is about the neurobiology of dopamine in an animal with chronic use of a drug 4. Study is about the neurobiology of serotonin in an animal with chronic use of a drug 5. Study is about the effect of ibogaine on cerebellar cell structure 6. Study is about the effect of ibogaine on motor function 7. Study is about the effect of ibogaine on cardiac rhythm	
	Study characteristics to be extracted (for assessment of external validity, reporting quality)		
27.	Study ID (*e.g.* authors, year)	Authors, title, journal, year, language, contact author e-mail	
28.	Study design characteristics (*e.g.* experimental groups, number of animals)	Nr of animals in experimental and control group, presence and type of control group, animal model used ? (addiction/healthy)	
29.	Animal model characteristics (*e.g.* species, gender, disease induction)	Species, strain, sex, weight, age, type of animal addiction model, aspect of addiction, type of drug, duration and dose of drug treatment	
30.	Intervention characteristics (*e.g.* intervention, timing, duration)	Route of administration, dose, frequency, duration treatment, timing treatment,.	
31.	Outcome measures	Timing of data collection, outcome measure behaviour (self-administration and place preference),neurobiology (dopamine and serotonin brain tissue levels),toxicology (purkinje cell death, GFAP stained cell death, motor	

		functioning)	
32.	Other (*e.g.* drop-outs)	-	
	Risk of bias assessment (internal validity)		
33.	Specify the number of reviewers assessing the risk of bias in each study	2	
34.	Define criteria to assess the internal validity of included studies (*e.g.* selection, performance, detection and attrition bias)	☐By use of SYRCLE's Risk of Bias tool [4] **X**By use of SYRCLE's Risk of Bias tool, adapted as follows: lack of selection of outcomes measures is not reported ☐By use of CAMARADES' study quality checklist, e.g. [5] ☐By use of CAMARADES' study quality checklist, adapted as follows: ☐Other, namely:	
	Collection of outcome data		
35.	For each outcome measure, define the type of data to be extracted (*e.g.* continuous/ dichotomous, unit of measurement)	Outcome measures that are continuous variables: Behaviour: selfadministration , place preference Neurobiology: Dopamine, serotonine brain tissue levels Toxicology: Cerebellar cell-loss, motor impairment Outcome measures that are dichotomous: Toxicology: Cerebellar cell-loss, motor impairment	
36.	Methods for data extraction/retrieval (*e.g.* first extraction from graphs using a digital screen ruler, then contacting authors)	1) extract data from text or tables 2) extract data from figures (digital screen ruler) 3) contact authors in case of missing data (max 2 emails)	
	Data analysis/synthesis. Specify (per outcome measure):		
37.	How you are planning to combine/compare the data (*e.g.* descriptive summary, meta-analysis)	Meta-analysis with subgroup analysis and sensitivity analysis for all outcome measures if possible otherwise descriptive summary	
38.	How the decision as to whether a meta-analysis will be performed will be made	Outcome data will always be pooled. No restrictions in terms of heterogeneity will be applied, instead, sources of heterogeneity will be investigated through sensitivity and subgroup analysis	
	If a meta-analysis seems feasible/sensible, specify for each outcome measure:		
39.	The effect measure to be used (*e.g.* mean difference, standardized mean difference, risk ratio, odds ratio)	For all continuous outcome measures: SMD For all dichotomous outcome measures: RR	
40.	The statistical model of analysis (*e.g.* random or fixed effects model)	Random effect model	
41.	The statistical methods to assess heterogeneity (*e.g.* I^2, Q)	I^2	
42.	Which study characteristics will be examined as potential source of heterogeneity (subgroup analysis)	Animal species, gender, duration of treatment, dosage of treatment, drug used in addiction model	
43.	The method for assessment of publication bias	Funnel plot, Duval and Tweedie's trim and fill analysis and	

44.	Any sensitivity analyses you propose to perform	duration of treatment, dosage of treatment,	
Final approval by (names, affiliations):			Date: 16-12-2014

Search strategy:

PubMed	"Ibogaine"[Mesh] OR ibogaine[tiab] OR noribogaine[tiab] OR 12-Methoxyibogamine[tiab] OR 12 Methoxyibogamine[tiab] OR NIH-10567[tiab] OR NIH 10567[tiab] OR Endabuse[tiab]
Embase	(exp ibogaine/OR (ibogaine or ibogain or noribogain or nor-ibogaine or nor-ibogain or noribogaine or NIH-10567 or "NIH 10567" or NIH10567 or Endabuse).ti,ab.)) *12-Methogyibogamine and 12 Methogyibogamine gives a syntax error in search string*
PsychINFO	(ibogaine or ibogain or noribogain or nor-ibogaine or nor-ibogain or noribogaine or NIH-10567 or NIH10567 or Endabuse).ti,ab. *12-Methogyibogamine and 12 Methogyibogamine gives a syntax error in search string*
CINAHL	TI (ibogaine OR ibogain OR noribogain OR nor-ibogaine OR nor-ibogain OR noribogaine OR 12-Methoxyibogamine OR “12 Methoxyibogamine” OR NIH-10567 OR “NIH 10567” OR NIH10567 OR Endabuse) OR AB (ibogaine OR ibogain OR noribogain OR nor-ibogaine OR nor-ibogain OR noribogaine OR 12-Methoxyibogamine OR “12 Methoxyibogamine” OR NIH-10567 OR “NIH 10567” OR NIH10567 OR Endabuse
Web of Science	Topic=(ibogaine OR ibogain OR noribogain OR nor-ibogaine OR nor-ibogain OR noribogaine OR 12-Methoxyibogamine OR “12 Methoxyibogamine” OR NIH-10567 OR “NIH 10567” OR NIH10567 OR Endabuse) *Databases=SCI-EXPANDED, SSCI, A&HCI Timespan=All Years; Lemmatization=On*