



# Pharmacological and methodological aspects of the separation-induced vocalization test in guinea pig pups; a systematic review and meta-analysis



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## ABSTRACT

The separation-induced vocalization test in guinea pig pups is one of many that has been used to screen for anxiolytic-like properties of drugs. The test is based on the cross-species phenomenon that infants emit distress calls when placed in social isolation.

Here we report a systematic review and meta-analysis of pharmacological intervention in the separation-induced vocalization test in guinea pig pups. Electronic databases were searched for original research articles, yielding 32 studies that met inclusion criteria. We extracted data on pharmacological intervention, animal and methodological characteristics, and study quality indicators.

Meta-analysis showed that the different drug classes in clinical use for the treatment of anxiety disorders, have comparable effects on vocalization behaviour, irrespective of their mechanism of action. Of the experimental drugs, nociception (NOP) receptor agonists proved very effective in this test. Analysis further indicated that the commonly used read-outs total number and total duration of vocalizations are equally valid. With regard to methodological characteristics, repeated testing of pups as well as selecting pups with moderate or high levels of vocalization were associated with larger treatment effects. Finally, reporting of study methodology, randomization and blinding was poor and Egger's test for small study effects showed that publication bias likely occurred.

This review illustrates the value of systematic reviews and meta-analyses in improving translational value and methodological aspects of animal models. It further shows the urgent need to implement existing publication guidelines to maximize the output and impact of experimental animal studies.

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## 1. Introduction

In the search for novel pharmacological treatment of anxiety disorders, a wide range of animal models and tests has been used. Anxiety tests may either be performed in naïve animals or in animals in which aspects of the disease are modelled, e.g. by genetic modification or exposure to traumatizing stimuli. Furthermore, the read-outs quantified in the test itself may be based on innate anxiety, conditioned fear or conflict behaviour.

As of yet, it is unclear to what extent these approaches differ in predicting potential clinical efficacy and in detecting potential druggable targets. Together with the still limited understanding of the pathophysiology of anxiety disorders, this lack of knowledge may have hampered the translation of preclinical findings to the clinic (see [Griebel and Holmes, 2013](#)). In addition, limitations in

study quality and design of experimental animal studies may also have contributed to this poor translation ([Landis et al., 2012](#)), notwithstanding issues concerning the outcome of clinical trials, such as high placebo responsiveness, patient selection and heterogeneity ([Zimmerman et al., 2002](#)).

As a first step to objectively characterize drug sensitivity and specificity of a particular anxiety test, we performed a systematic review and meta-analysis on pharmacological interventions in the separation-induced vocalization test in guinea pig pups and characterized methodological factors that may affect test outcome. In view of the concerns regarding study quality of experimental animal studies ([Landis et al., 2012](#)), we also determined prevalence of reporting of measures to reduce risk of bias and aimed to characterize if biases in publication are likely to occur.

The separation-induced vocalization test in guinea pig pups is based on the fact that pups emit distress calls when involuntarily separated from mother and littermates ([Herman and Panksepp, 1978](#); [Pettjohn, 1979a, 1979b](#)). Narrative reviews indicate that, in contrast to other tests, the guinea pig pup vocalization test is sensitive to a broad range of antidepressants agents with anxiolytic properties

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(Sanchez, 2003; Borsini et al., 2002). This is an important observation in light of the highly valued predictive validity of animal models (Willner, 1984; Markou et al., 2009). Clinically, antidepressants are prescribed more frequently, and are preferred over benzodiazepines for the treatment of anxiety disorders (Baldwin et al., 2014; Chessick et al., 2006), although the evidence to support this has recently been questioned (Offidani et al., 2013; Rickels, 2013).

Besides detecting anxiolytic properties of antidepressant compounds, the guinea pig pup vocalization test has some additional valuable features. For certain neurotransmitter systems, human receptor pharmacology is more akin to that of guinea pigs than that of rats and mice, e.g. substance P (neurokinin (NK)<sub>1</sub> receptors (Rigby et al., 2005; Kramer et al., 1998; Leffler et al., 2009) and the serotonergic system (5-HT<sub>1B</sub>, 5-HT<sub>1D</sub> receptors (Sipes and Geyer, 1996). In addition, brain development in guinea pig pups is in a more advanced state than that of rodents at birth (Clancy et al., 2007). Finally, the test induces relatively low discomfort to the animals, is easy to perform, and does not require special equipment, as guinea pig pups emit mainly audible calls upon separation (400–20,000 Hz; Berryman, 1976), which can easily be quantified. Together, these observations make this test interesting to further characterize pharmacologically and methodologically.

As outcome measures for our evaluation of drug efficacy in the separation-induced vocalization test in guinea pig pups, we used the total number and total duration of emitted vocalizations during social isolation. In the meta-analysis, we only included drugs that were hypothesized to reduce vocalization behaviour, whereas the systematic review was not confined to particular drug actions.

Literature suggests that both baseline levels of anxiety as well as sensitivity to the anxiolytic-like action of drugs in rats and mice are influenced by factors including strain (Griebel et al., 2000; Van Bogaert et al., 2006), early life stress (Paris and Frye, 2011; Schopper et al., 2011; Van Bogaert et al., 2006; Groenink et al., 2011) and environmental enrichment (Hendriksen et al., 2012). To determine if these factors affect drug efficacy in guinea pigs as well, we included these factors in our study. As behavioural studies indicate that age (Hennessy and Ritchey, 1987; Arch-Tirado et al., 2000), duration of social isolation (Monticelli et al., 2004), successive disturbances (Hennessy et al., 2006; Arch-Tirado et al., 2000), test environment (Hennessy and Ritchey, 1987) and presence of other guinea pigs in the test room (Pettijohn, 1979a), may influence vocalization behaviour in guinea pigs, we extracted information related to these factors as well. In addition, we studied if selection of pups based on pre-test vocalization levels, and repeated testing of animals impacted on study precision and effect size.

Finally, with regard to study quality, we assessed whether randomization, blinding and sample size calculations were reported and

performed, since these factors are key in reducing the risk of biased results (Landis et al., 2012).

## 2. Material and methods

The systematic review was performed following a predefined protocol, the conditions of which are outlined below.

### 2.1. Literature search and study selection

Studies reporting drug treatment effects in separation-induced vocalization tests in guinea pigs were identified by electronic searching of Medline (via PubMed), Embase and Scopus, on January 14th, 2014. The search strategy was broad: it was designed to identify any study which measured vocalization behaviour in guinea pigs, it was not restricted by pharmacological intervention or language (for details see Table 1).

We applied the following criteria for in- and exclusion of peer-reviewed, original research articles:

- Only studies using *guinea pigs* were included. All strains of guinea pigs were eligible, regardless of age and sex.
- Only studies describing *effect of drug treatment on separation-induced vocalizations* compared with *control animals receiving vehicle treatment* were included.
- Studies using a *systemic route of drug administration* were included. Studies using *intra-cerebral or local infusion in specific brain areas* were excluded.
- Studies describing drug effects in animals that had received previous treatment, stress manipulations, lesions in the central nervous system or other treatments aimed at altering baseline levels of vocalizations were excluded.
- Review articles not reporting original data were excluded.
- If sufficient information to compute effect sizes could not be obtained from the article or from the primary or last author, studies were excluded from the meta-analysis.

To identify articles meeting the inclusion criteria (see Section 2.2), abstracts of retrieved articles were independently screened by two investigators (MV, LG), using EROS 3.0 (Early Review Organizing Software, Institute of Clinical Effectiveness and Health Policy, Buenos Aires, Argentina). Discrepancies were solved by discussion among the two investigators. In case information provided in the abstract was insufficient to decide upon in- or exclusion, both investigators screened the full article, following the same procedure.

**Table 1**  
Search terms used to identify relevant articles.

Data base	Search string	Hits
PubMed	((“Guinea pigs”[MeSH Terms] OR (“guinea”[All Fields] AND “pigs”[All Fields]) OR “guinea pigs”[All Fields] OR (“guinea”[All Fields] AND “pig”[All Fields]) OR “guinea pig”[All Fields]) OR (“guinea pigs”[MeSH Terms] OR (“guinea”[All Fields] AND “pigs”[All Fields]) OR “guinea pigs”[All Fields] OR “cavia”[All Fields]) OR (“guinea pigs”[MeSH Terms] OR (“guinea”[All Fields] AND “pigs”[All Fields]) OR “guinea pigs”[All Fields] OR (“cavia”[All Fields] AND “porcellus”[All Fields]) OR “cavia porcellus”[All Fields]) OR (“guinea pigs”[MeSH Terms] OR (“guinea”[All Fields] AND “pigs”[All Fields]) OR “guinea pigs”[All Fields])) AND (Vocalization[All Fields] OR Vocalizations[All Fields] OR call[All Fields] OR calls[All Fields] OR (Distress[All Fields] AND vocalization [All Fields]) OR (Distress[All Fields] AND vocalizations[All Fields]))	201
Embase	(‘Guinea pig’/exp OR ‘guinea pig’ OR ‘cavia’/exp OR ‘cavia’ OR ‘cavia porcellus’/exp OR ‘cavia porcellus’ OR ‘guinea pigs’/exp OR ‘guinea pigs’) AND (‘vocalization’/exp OR ‘vocalization’ OR ‘vocalizations’ OR ‘distress vocalization’ OR ‘distress vocalizations’ OR ‘call’ OR ‘calls’ OR ‘vocalization’ OR ‘vocalizations’)	208
Scopus	(TITLE-ABS-KEY-AUTH(guinea pig) OR TITLE-ABS-KEY-AUTH(guinea pigs) OR TITLE-ABS-KEY-AUTH(cavia porcellus) OR TITLE-ABS-KEY-AUTH(cavia) AND (TITLE-ABS-KEY-AUTH(Vocalization) OR TITLE-ABS-KEY-AUTH(Vocalizations) OR TITLE-ABS-KEY-AUTH(Distress vocalization) OR TITLE-ABS-KEY-AUTH (Distress vocalizations) OR TITLE-ABS-KEY-AUTH(Call) OR TITLE-ABS-KEY-AUTH(Calls) OR TITLE-ABS-KEY-AUTH(Vocalization) OR TITLE-ABS-KEY-AUTH (Vocalizations)))	255

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