

Side effects of drugs studied on ant models: a mini review

Abstract

Using ants as models, we studied until now the side effects of 47 products used by humans and, over these studies we published five summaries of our main findings. After that, we studied the side effects of six other drugs used by humans, and we here summarize these lastly obtained results. These six other drugs were dextromethorphan, amitriptylin, escitalopram, fluvoxamine, iverectin, and indapamide. For each of them, we found side effects similar to those reported for humans, but we also observed side effects not yet mentioned for humans. They concerned among others the locomotion, the activity, the sensory perception, the social relationships and the learning. Practitioners and pharmacists should take cognizance of our works for more adequately and safely used the six drugs we examined. Our six works are published and thus available, but they can also be provided by the author(s). All over our studies, ants appeared to be excellent biological models; the experiments could be made easily, rapidly and at lost cost, while providing statistically significant results.

Keywords: amitriptylin, cognition, dextromethorphan, escitalopram, fluvoxamine, indapamide, ivermectin, social interactions

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Abbreviations: ang.deg./cm, angular degrees per centimeter; cm, centimeter; mm, millimeter; mm/s, millimeter per second; mg, milligram; ml, milliliter; χ^2 , chi square; df, degree of freedom; P, level of probability

Introduction

Medicinal drugs, though often essential for ill humans, have generally side adverse effects which must be known and taken into account during the patients' treatment. Using ants as models, we examined such side effects of until now 47 drugs, and, for the readers' convenience, in addition to the publication of each of these works, we summarized our main findings in up to day five papers.¹⁻⁵ After our last published summary, we still examined the side effects of six drugs,⁶⁻¹¹ and we here summarize these new results in a sixth short paper. Working on ants as models, we could precisely defined some kinds of effects, such as those on the individuals' movement, sensory perception, social interactions, cognition, memorization, and could inform on the individuals' adaptation to these effects and on their dependence on the drug consumption. We could also explain how (the manner according which) the drug loses its effect after weaning. All this can be useful to practitioners and pharmacists. The six drugs, the side effects of which we studied and here summarized are, successively, dextromethorphan, amitriptylin, escitalopram, fluvoxamine, iverectin, indapamide. Before relating our works, we below report medicinal information about these six largely used drugs.

Dextromethorphan is the dextrogyre enantiomer of levomethorphan which is an opioid analgesic. It acts as a central cough suppressant.¹² Assessing the efficiency of dextromethorphan and codeine *versus* placebo revealed that the two products significantly reduce the cough intensity.¹³ Other clinical studies also pointed out the efficiency of dextromethorphan (e.g.^{14,15}) while other ones did not (e.g.^{16,17,18}) maybe due to the smallness of the samples. Adverse effects have been mentioned for dextromethorphan consumption¹⁹ such as nausea,

blurred vision, dizziness, sedation, cases of overdose which led to addiction,²⁰ paranoia,²¹ decrease of motor coordination.²² Nothing is reported as for the impact of dextromethorphan on the individuals' cognition, learning, memorization, social relationships and adaptation to side effects, a gap our work on ants tempted to fill.

Amitriptylin is an antidepressant belonging to the less toxic category, the TCA (tricyclic) one. It seems to be rather efficient with not severe side effects,²³ and it also allows treating children's urinary-incontinuity.^{24,25} The most observed side effects of amitriptylin are e.g. behavioral impairments, tiredness, confusion, headache, and thirst. Working on ants, we brought information on its effect on, among others, the individuals' locomotion, social relationships, cognition, adaptation, habituation and dependence.

Escitalopram is also an antidepressant, but more efficient and causing more adverse effects than amitriptylin. It is an inhibitor of the serotonin recapture (an ISSR). Nowadays, due to the social troubles caused by the Covid-19 pandemic, more and more persons need such 'strong' antidepressants. Escitalopram has been proved to be efficient,^{26,27,28} even for elderly persons,²⁹ and to be rather well tolerated by patients.^{30,31} However, several impairments caused by its consumption are reported in the notice joined to escitalopram packages. Among these impairments, let cite headache, muscular pain, tiredness, visual perception problems, aggressiveness, confusion. Nothing is mentioned as for the impact of the drug on the individuals' locomotion, social relationships, cognition, learning, memorization, adaptation, dependence, and loss of effects after weaning. For filling this gap, we examined as usually the impact of escitalopram on ants' physiological and ethological traits.

Fluvoxamine is again an ISSR antidepressant, efficient,^{32,33} but it can also be used for treating non depressive central nervous system disorders,^{34,35,36} and it was recently found to help caring of persons suffering from the Covid-19 illness.^{37,38,39} Information on fluvoxamine can be found in the reviews.^{40,41} Nevertheless, little information on

the impairments of this drug is available, and we thus studied such potential effects of fluvoxamine on ants' physiological and ethological traits, as usually.

Ivermectin, a macrocyclic lactone, is an efficient antihelmintical drug used for caring of patients suffering from, among others, loaloase, onchocerciasis,^{42,43} as well as galla,⁴⁴ and it was exceptionally found (it is an example of serendipity!) to help treating persons suffering from the Covid-19 illness,^{45,46} even if this is not yet unanimous admitted.⁴⁷ Though the side effects of ivermectin occurring during antihelmintical treatments are rather well known (e.g. treated persons suffer from weakness, drowsiness, tremors, mental disorders),^{48,49} those which may appear in patients treated for their Covid-19 illness have not yet been carefully, sufficiently examined. We thus studied, as usually, potential impacts of ivermectin on several physiological and ethological traits of ants.

Indapamide is a sulfonamide used for caring of persons suffering from hypertension, edema, or some heart disfunctioning^{50,51,52,53} and appears to be efficient.^{54,55} In the notice joined to this drug packages, several side effects are mentioned, e.g. headache, tiredness, weakness, tottering. Since indapamide decreases the levels of sodium and potassium,⁵⁶ it may alter the ionic blood concentration and consequently affect several physiological and ethological traits not considered in the notice nor on internet links devoted to this drug. We thus studied such potential impacts of indapamide on ants as models; we examined their adaptation to and their dependence on indapamide, and we defined the loss of the effect of indapamide after weaning.

In the discussion section, two other drugs, the effects of which we did not studied, are also mentioned and commented.

Material and methods

Since we have largely explained our experimental protocols in 47 works on drugs side effects, and since the present paper summarizes six new such works which again report these protocols, we here only very briefly relate these many times used and explained protocols.

Collection and maintenance of ants

The ants have been collected from several regions located in Belgium: the Aise valley (Ardenne), Olloy-sur-Viroin (Ardenne), Marchin (Condroz) and Visé (Basse-Meuse). Each colony was maintained in 1 to 3 glass tubes which contained water and a cotton plug. These tubes were set in a tray in which food, consisting in sugar water and *Tenebrio molitor* larvae, was delivered several times per week. The lighting of the laboratory was 110 lux while not working on ants, and 330 lux when caring of or experimenting on them. The humidity equaled about 80%, the temperature 20°C and the electromagnetic field $2\mu\text{Wm}^2$.

Drugs supply and drug solutions given to the ants

The six studied drugs were provided by the pharmacist Wera (whose pharmacy is located at 1170 Bruxelles, Begium), in their standard package which contained the notice for their use. A given amount of each drug was duly crushed and dissolved in a precise volume of sugared water, in order to obtain a solution ten times more concentrated than the solution daily consumed by humans. Indeed, insects and thus ants, due to their anatomy and physiology, drink ten less water than mammals including humans. The drug solution was given to the ants in their usual cotton plugged tubes. The plug was humidified and the entire solution renewed as necessary.

Traits examined in ants

The physiological and ethological traits which could be impacted by the drugs and which we examined on ants were the meat intake, sugar water consumption, general activity, linear and angular speeds of locomotion, orientation ability, audacity, tactile (pain) perception, brood caring, social relationships, stress and cognition (through escaping behavior), cognition (through the ability to cross a twists and turns path), conditioning acquisition, memory, adaptation to the side effects of the product, habituation to its wanted effect if possible, dependence on the drug consumption, decrease and loss of the effect of the drug after its consumption was stopped. For each studied drug, their impact on all these traits has been examined. However, since the present paper is a summary of our findings, only the most important impacts are here reported.

Assesment of the ants' traits

Each trait was assessed according to a protocol and a statistical analysis set up since eight years and explained in 53 publications (47 already published in 5 summaries and 6 summarized in the present paper). Re-describing our methods would be redundant and would burden the present summary. We invite readers to take cognizance of our experimental processes in our previously published paper.⁶⁻¹¹

Results

Dextromethorphan

This cough drug appeared to reduce the ants' food intake and general activity. It also enlarged their sinuosity of movement and reduced their tactile (pain) perception. Dextromethorphan affected the ants' brood caring and their normally peaceful relation with congeners, impacting thus their social relationships (Table 1, line 1). No adaption occurred over the short lasting time period of the experimental work. The cough drug did not affect the ants' state of stress, cognition, conditioning acquisition and memorization. Unfortunately, the drug led to dependence, the ants preferring a solution containing the drug to a drug-free solution (Figure 1 A). The effect of dextromethorphan linearly vanished in 10 hours (so rather rapidly) after weaning, according to the linear function:

$$E_t = E_i - 8.17 t \text{ with } E_t = \text{effect at time } t; E_i = \text{initial effect and } t = \text{time in hours.}$$

All this leads to some comments reported in the discussion section.

Amitriptylin

The antidepressant amitriptylin had a lot of side effects in ants. It decreased their food intake, general activity, locomotion, orientation ability, tactile (pain) perception, brood caring and aggressiveness between congeners (Figure 1 B) and so their social relationships, their cognition, ability to escape from an enclosure (Table 1, line 2), and conditioning acquisition. The ants slowly, slightly adapted themselves to the effects of amitriptylin and became habituated to them. They did not develop dependence on this drug consumption. The drug had still some effect 33 hours after weaning and fully lost its effect in a total of 36 hours according to the function: $E_t = E_i - 2.5 t$ with $E_t = \text{effect at time } t; E_i = \text{initial effect and } t = \text{time in hours.}$

So many adverse effects should be considered when treating humans with amitriptylin, an advice commented in the discussion section.

Table 1 An observed effect (on twelve examined ones) for each of the six studied drugs

Drug, examined trait	Normal diet	Diet with the drug
Dextromethorphan: aggressiveness between congeners	a = 0.14	a = 0.79
Amitriptylin: number of ants among 12 escaped in 12 minutes	12	3
Escitalopram: number of ants in front and beyond a twists and turns path after 12 minutes	in front: 11 beyond: 7	in front: 16 beyond: 2
Fluvoxamine: mean numbers of ants active, on the meat, and on the sugar water	12.67 1.71 1.96	4.38 0.46 0.50
Ivermectin: ants' linear speed	10.3 mm/s	6.0 mm/s
Indapamide: score after 72 training hours	85%	90%
score 72 hours after the cue removal	80%	80%

Some more information is given in the results section, and all the available one can be found in the six works relative to these drugs.⁶⁻¹¹ The observed effects reported in the table successively concerns the aggressiveness between nestmates, the escaping ability, the ability to cross a difficult path (i.e. the cognition), the general activity and the food consumption, the linear speed, the learning and memorization. The five first traits were decreased by the drug; the sixth one was not impacted. mm/s = millimeter per second; % = percentage

Excitalopram

Being an ISSR antidepressant, excitalopram of course caused many side adverse effects. It decreased the ants' food intake, general activity, locomotion, orientation ability, tactile (pain) perception, brood caring and aggressiveness towards nestmates (impacting so their social relationships), their cognition (Table 1, line 3; Figure 1 C) and conditioning acquisition. The ants did not adapt themselves to these side effects, but did not become dependent on escitalopram consumption. After weaning, the effect of escitalopram stayed significantly similar to its initial one during 18 hours, became different from it though still differing from the control situation during a total of about 30 hours, and fully vanished in 36 hours. This decrease could be best described by the linear function: $E_t = E_i - 1.33 t$ with E_t = effect at time t ; E_i = initial effect and t = time in hours.

Comments on these findings and comparison with other researchers' observations are given in the discussion section.

Fluvoxamine

Fluvoxamine, a SSRI antidepressant nowadays also used for caring of persons suffering from the Covid-19 illness, induced several adverse effects in ants. It decreased these insects' food intake (Table 1, line 4), largely impacted their locomotion (Figure 1 D), orientation ability, audacity (Figure 1 D), tactile (pain) perception, brood caring and aggressiveness against nestmates (so their social relationships), their cognition, their conditioning acquisition and thus their short-term memory. The ants did not adapt themselves to these side effects: they were still largely affected after ten days under the drug diet. The ants did not develop dependence on fluvoxamine consumption. After weaning, the effect of fluvoxamine slowly decreased: it kept its effect during about 12 hours, had then a slight effect during 6 more hours, and reached a non-significant effect in 3 more hours. The drug entirely lost its effect in 12 more hours, so in a total of 33 hours. This decrease could be best described by the quadratic function:

$E_t = 198.76 - 1.13 t - 0.03 t^2$ with E_t = effect at time t ; t = time in hours (and $R^2 = 0.984$)/

In the discussion section, these findings are commented and compared with those available in the literature.

Ivermectin

Ivermectin, an efficient antihelminthical drug which was recently successfully used for caring of persons suffering from the Covid-19,

had several side effects in ants. It decreased or impacted these insects' meat and sugar water intake, activity, locomotion, orientation ability, tactile (pain) perception, brood caring and relations with nestmates, cognition and short-term memory (Figure 1 E). The ants did not adapt themselves to these side effects, but did not develop dependence on ivermectin consumption. After weaning, the drug kept its effect during 5 hours, and then partly lost it during 12 more hours though still differing from the control situation. The effect of the drug became statistically similar to the control one in 7 more hours, and the drug entirely lost its effect in 6 more hours. Therefore, the effect of ivermectin fully vanished in a total of 30 hours, and this occurred according to a quadratic function that could be written like:

$$E_t = E_i - t^{0.022}$$

with t = time (in hours), E_t = effect at time ' t ', E_i = initial effect

Comments, comparison with available information on the drug use and advices for its use are given in the discussion section.

Indapamide

The drug indapamide, used in humans for treating hypertension, edema and cardiac problems, caused a few physiological and ethological impairments in ants. It significantly reduced or impacted their food intake, general activity, audacity, sensory (tactile and olfactory (Figure 1 Fb) perception, brood caring (Figure 1 Fa) and interaction with congeners (so their social relationships). Indapamide did not affect the ants' state of stress, cognition (Figure 1 Fc), conditioning acquisition and memorization (Table 1, line 6). The ants never adapted themselves to the side effects of the drug, but they developed no dependence on its consumption. After weaning, the effect of indapamide firstly slowly decreased, being still similar to the initial one after 8 hours. It then stayed different from the control situation during 8 more hours. After that, it somewhat more rapidly decreased and vanished in 8 more hours. Indapamide lost thus fully its effect in a total of 24 hours according to a quadratic function of the time that could be written as:

$$E_t = E_i - t^{0.03}$$

with t = time (in hours), E_t = effect at time ' t ', E_i = initial effect.

During this decrease, as well as during the study of each examined trait, a large individual variability was observed. Humans should be best treated case-by-case. This advice and some comments about the use of indapamide are given in the discussion section.

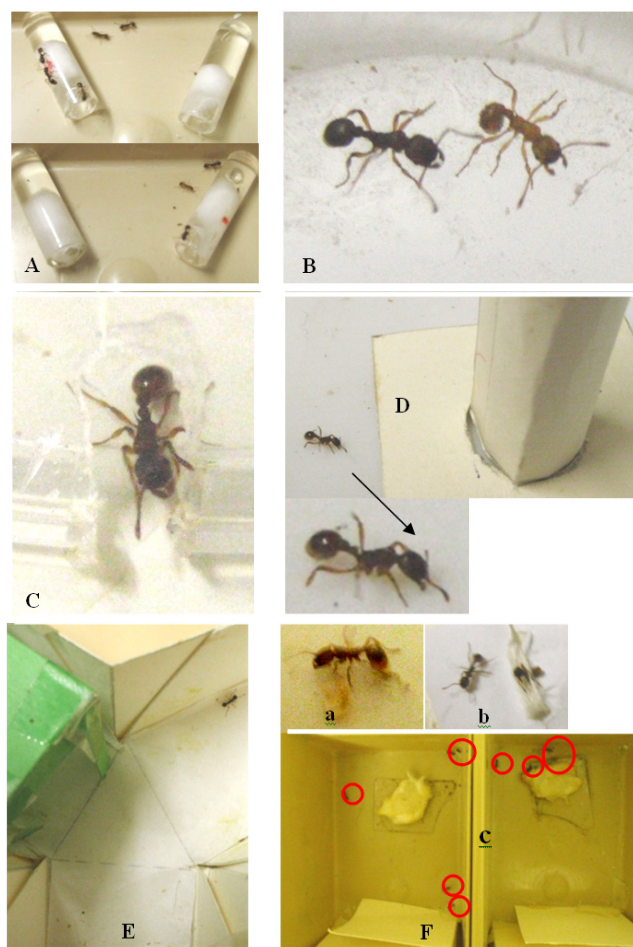


Figure 1 A few photos of the experiments made for examining the side effects of six drugs. More ones can be found in.⁶⁻¹¹

A: ants consuming dextromethorphan became dependent on this drug (red dot).

B: two nestmates under amitriptyline diet exhibiting aggressive behavior.

C: an ant under escitalopram diet not escaping from an enclosure.

D: an ant under fluvoxamine diet not coming on a risky apparatus and walking with difficulties.

E: an ant under ivermectin diet, trained to a green cube, and giving the wrong response when tested in a Y-apparatus.

F: ants under a diet with indapamide successively:

a: not taking care of a larva,

b: not orienting itself towards a tied nestmate,

c: having been able to cross a twists and turns path.

Discussion

Below, we comment and compare our results with those available in literature.

Concerning dextromethorphan, an excellent agreement could be observed between our findings and the information available on the side effects of this cough drug. Also, our results about the ants' dependence on dextromethorphan and the loss of the drug effect after weaning were in agreement with what is observed in humans respectively.^{57,58} Attention must thus be paid to humans consuming dextromethorphan in order to prevent them from becoming dependent on it. Finally, let us add that natural products such as honey, thyme,

propolis, can calm cough, and that cough is a vital reflect which allows clearing congested respiratory track.

Amitriptylin is an antidepressant also used for treating children's urinary-incontinency troubles and some neuropathic pains. It allows preventing migraine better than other drugs,⁵⁹ but presents harmful side effects.⁶⁰ Our work in ants confirmed the existence of these side effects and moreover revealed the potential occurrence of a few other ones. Therefore, since amitriptylin is an efficient drug less toxic than other stronger antidepressants, it should be used, but at widely spaced doses, and the patients should be monitored as for their food intake, social relationships, cognition, memory, and habituation to the positive effect of the drug.

Escitalopram is an efficient antidepressant with apparently less toxic effects than other similar drugs.⁶¹ Nevertheless, it had adverse effects in ants, and those we found are in agreement with those reported in the literature.^{62,63,64} In ants, we could not examine the individuals' potential habituation to wanted effects of the drug. Therefore, this should be studied in humans because if habituation occurs, humans will be tempted to increase their daily dose what would accentuate the drug side effects.

Fluvoxamine is an efficient antidepressant and may soon be used for treating the Covid-19 illness; it is a valuable drug.^{40,41} However, in ants, we found it induced many severe effects. Some of them have been reported in humans;^{65,66,67} other ones have not yet been observed, but they may occur. Therefore, we advise to monitor patients treated with fluvoxamine as for their appetite, activity, sensory perception, social relationships, cognition and memorization. Also, it should be checked if these patients become habituated to the researched effect of fluvoxamine, because if this occurs, the patients will be tempted to increase their drug dose, and doing so would accentuate the drug side effects. In addition, some concordance appeared between our findings on the loss of the effect of fluvoxamine after weaning and what was observed as for this topic in humans.^{68,69} On the basis of these findings, we propose to care of patients thanks to a daily dose of 100 g every 36 hours (and not every 24 hours as it is currently the case), what would allow limiting the drug side effects.

The side effects of ivermectin used as an antihelmintical drug are rather well known, but those which may occur while using it to treat persons suffering from or susceptible to contract the Covid-19 are not precisely known until now. Ants maintained under an ivermectin diet presented several physiological and ethological impairments which may occur in humans. Therefore, before massively using ivermectin, we recommend to make duly conducted medicinal studies in order to examine the occurrence of side effects and to define the most appropriate daily dose. As for this last point, the decrease of the wanted effect of ivermectin should be established, and patients' potential habituation to such wanted effect should be examined. In addition, ivermectin is very toxic for the environment, especially for the insects.⁷⁰ Systems for eliminating the drug residues from waste water should be set up before world widely using it for significantly decreasing the nowadays Covid-19 pandemic.

Due to its mode of action and its low diuretic effects, indapamide had in ants not much severe adverse effects, what is also the case for humans.^{50,51,52} For instance, indapamide did not impact the ants' cognition, learning and memorization. This finding is in agreement with the improved impact of the drug on the brain functioning of patients having had cerebrovascular diseases.⁷¹ Nevertheless, we found that indapamide had several side effects which should be examined in humans. These effects are, among others, impairments of food intake, activity, locomotion, sensory perception, and social relationships.

These effects may be due to the lowering of the calcium and the potassium levels induced by the drug.⁵³ In addition to the exam in humans of the side effects observed in ants, we estimate that humans' potential habituation to the researched effect of indapamide should be examined, and that patients should be treated case-by-case (e.g. for defining their daily dose) since in ants a large individual variability has been observed. *Even if not editable, we want to affirm that, being under an indapamide diet since one year, we very obviously feel some changes in our physiology and ethology fully in agreement with what we found in ants. We suffer from tiredness, weakness while moving, and have some social relationships troubles, no longer appreciating the presence of parents and friends.*

To finish, we give our opinion on two drugs we did not studied since they are not yet available in Belgium (our country), but which may soon be used to treat patients suffering from the Covid-19 illness. Peritonitis of felines is due to a corona virus and is treated thanks to the drug remdesivir. Therefore, practitioners have tried to use this drug for caring of humans having the Covid-19 illness. Remdesivir seemed to be rather efficient,⁷² but this must yet been confirmed through uses of the drug and medicinal experimentations. We want to point out that domestic cats often suffer from kidney illness and that, unfortunately, for cats, remdesivir appeared to be toxic for this organ. Consequently, remdesivir should no longer be used for caring of cats suffering from peritonitis. Molnupiravir is a drug newly used for treating the Covid-19,⁷³ but more essays, medicinal researches and observations are required for affirming its efficiency. Nevertheless, due to its mode of action, this drug largely reduces the propagation of the virus, and is thus very promising.

Conclusion

After having published five summaries relating our previous studies of 47 products used by humans, we here present a summary of our six last studies on drugs. We used ants as models, as usually, confirmed the side effects observed in humans, and revealed other not yet observed ones. Practitioners and pharmacists should take our findings and advices into account while using one or the other of these six drugs. The present work is only a summary, a 'mini review'; the entire works are published in⁶⁻¹¹ and can be asked directly to the author(s). Using ants as models turned out being successful, not expensive, rather easy, and moreover presenting very little ethical consideration. A final advantage would be to provide significant information to medical science.

Our future research projects are the studies of diuretics having less side effects than indapamide, of novelty used antidepressants (the consumption of which nowadays increases), and of drugs recently used for caring of persons suffering from the Covid-19 which still spreads.

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Conflicts of interest

We declare having no conflict of interest as for the manufacture, the sell and the use of the drugs we studied. We work on ants, on their behavior, cognition and ontogenesis of abilities, we use them as biological models for studying products consumed by humans, and we receive no money for making our research.

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