Foreground and background: an interview with Peter Singer and three arguments against naturalism

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Summary

The first part of this paper reports an interview with the philosopher Peter Singer. In the second, we examine Singer's background: naturalism and neurophilosophy, discussing three of its theses, as presented by Patricia Smith Churchland. Finally, we go back to Singer himself, to draw some conclusions.

KEY WORDS: mind/body problem, naturalism, neurophilosophy, Patricia Smith Churchland, Peter Singer, reductionism.

Introduction

Peter Singer, who is of Austrian Jewish origin, is one of the most widely known and important contemporary philosophers. He is 71 and married. His academic career has taken him to a number of prestigious universities, such as Melbourne, Oxford, Princeton and NYU. His books, mostly dealing with moral philosophy, are read all over the world and contribute to debate on topics in a range of areas, such as bioethics, animal rights, equality and charity towards poor countries. His ethical reflection revolves around the central, utilitarian, principle of maximizing the general amount of pleasure and thereby reducing the amount of suffering. According to this principle, the faculty to perceive pain and pleasure is enough to render a subject worthy of moral consideration. In line with this view, an animal may be considered worthy and a gravely malformed child not. However, in the following interview, which Mr. Singer granted me, I focused more on theoretical concerns than on specific ethical issues (for a recent and biographically detailed interview, see: Sosis, 2017).

Interview

A.L. Well, Mr. Singer, let us begin with a very direct shot: how does it feel to be considered, at least in the English-speaking philosophical world, one of the most influential living thinkers, known for your ability to "bite the bullet"?

P.S. I'm very pleased that my work is influential, because most of what I write is directed towards persuading people to act so as to reduce the amount of suffering in the world. So if I am having some influence in that direction, it's good for the world, and of course, fulfilling for me.

A.L. Would you like to sum up the story of your encounter with philosophy?

P.S. It's hard to sum up fifty years of studying, discussing and writing philosophy, but I've always wanted to make the work I do in philosophy relevant to important problems that we face, as individuals, societies or globally.

A.L. Nowadays, more than ever, philosophy seems to be facing an identity crisis. There is a dizzying variety of methods and schools of thought, far more, I assume, than in other disciplines like physics or literature. What exactly are, in your opinion, the methods and the tasks of philosophy, if it is to be understood as a coherent discipline?

P.S. I'm not bothered with trying to categorize philosophical methods or schools of thought. My area is ethics, and that means that I try to think clearly and deeply about how we ought to live, and what we ought to do. I'm interested in making good arguments, and showing the flaws in poor arguments, and I'm open-minded about how to do that.

A.L. Let me now ask a very brutal question: how can you still support utilitarianism after traversing the depth and the breadth of thinkers like Hegel and Marx, on whom you wrote two books?

P.S. Hegel and Marx both have interesting things to say, but as I explain in the two books you mention, they both say things that are clearly mistaken. Utilitarianism rests on more plausible foundations. I've tried to explain that in my most recent book, Utilitarianism: A Very Short Introduction, co-authored with the Polish philosopher Katarzyna de Lazari-Radek. Incidentally, all three of these books, Marx, Hegel, and Utilitarianism are in the same series, OUP's Very Short Introductions, and each one of them can be read in two hours or less, so I invite your readers to compare the arguments (Lazari Radek and Singer, 2017; Singer, 2000; Singer, 2001).

A.L. Let us move on to more specific topics. The main focus of your philosophical reflection is ethics, and indeed Practical Ethics could be considered your main philosophical work. Why this primacy?

P.S. As I said, I'm interested in areas of philosophy that can make a difference to the world, and I've seen, literally hundreds of times, how work in ethics can change

lives. Other areas of philosophy are intellectually intriguing, but given that we are living in a world with an immense amount of avoidable suffering in it, the fact that a problem is intellectually intriguing isn't sufficient justification to spend one's life working on it.

A.L. The magazine The New Criterion recently published an article entitled "What makes life worth living? Well, not Peter Singer" (Schick 2017). The Author portrays you as an arrogant and needlessly provocative academic with a flat prose style and basically no idea on what real life is. What would you say in response to this?

P.S. I haven't read the article to which you are referring, but I've never been needlessly provocative, and I've never defended a position that I do not think has strong arguments in its favour. If I have no idea what real life is, it's strange that so many people have changed their lives on the basis of my writing — doing things like becoming vegetarian or vegan, or donating a substantial proportion of their income to charities helping people in extreme poverty. As for my prose style, I suppose that's a matter of taste, and your readers should pick up one of my books and judge for themselves.

A.L. In a debate you conducted with the mathematician and Christian apologist John Lennox (Lennox and Singer, 2016), I had the impression that, for the entire time, the point was being missed. In my opinion, science cannot dismiss religion, and religion does not need science. They are two different fields and should be regarded as distinct; therefore reducing religion to science seems to make as little sense as reducing Mozart's Requiem to just a series of sound waves striking the ears.

P.S. I don't agree. Mozart's Requiem makes no claims about the world. In contrast, most religious believers do hold that their religion makes true claims about the world. They believe that there is a god, that certain writings are divinely inspired, and so on. Philosophical and science-based arguments are relevant to the truth of these claims.

A.L. In your opinion theism cannot explain undeserved suffering of children and animals. Let me turn the issue upside down and ask you: how can you explain undeserved suffering on the basis of your utilitarianism? To put it bluntly: can people really be so short-sighted as to refuse to increase the general amount of pleasure, or even so evil as to commit acts such as the holocaust? Don't you think that there is something more than pain and pleasure at stake here?

P.S. Utilitarianism is a normative theory. That means it tells us what we ought to do. Neither utilitarianism nor other normative theories attempt to describe the world, or, as you put it, "explain undeserved suffering." Utilitarianism is not committed to any view about whether people are foolish or sensible, compassionate or selfish.

A.L. Thank you for your replies, Mr. Singer, this has been a fascinating exchange of ideas. It is perhaps appropriate to end with a Hegelian conclusion: of course there are different and even opposite positions in philosophy — and this is precisely what absolute knowing is about: grasping opposing ideas together.

Foreground and background

In the following paragraphs, I shall examine Singer's neurophilosophical background, which underpins some of his theses. Indeed, in his philosophical thought, the state of the nervous system is crucial in order to determine the moral significance of a subject, and his argument against anti-specism, which started 20th century debate on animal rights (Magni, 2011), is based on the neurological consideration that animals can feel pain and pleasure (Singer, 1990). So, to use a cinematic analogy, at this point in this article the camera switches from the foreground (Singer himself) to the background.
The recent growth of knowledge about the brain has given rise to a philosophical approach called neurophilosophy. Patricia Smith Churchland has published a number of interesting articles on this topic, also for this journal. Essentially, neurophilosophy may briefly be defined as follows: «Neurophilosophy embraces the hypothesis that what we call "the mind" is in fact a level of brain activity. A corollary of this hypothesis states that we can learn much about the reality of mental function by studying the brain at all levels of organization» (Churchland, 2007). Moreover, neurophilosophy is a naturalistic philosophy, i.e. one that dismisses a priori knowledge and does not differ from science «either in the status of its theories or in its ultimate dependence on empirical data» (Churchland, 2008b).
If this holds true, we can consider Singer part of this movement, as well as many other prominent figures like Richard Dawkins, Stephen Hawkins, Daniel Dennett etc., who share this same conceptual background. They are, of course, different thinkers, but there is a sense of similarity between them nonetheless (for a different, milder version of neurophilosophy see Northoff, 2001; Northoff, 2013).
As always in history, science presents philosophy with major intellectual challenges. To quote the best known examples: the scientific revolutions of Galileo, Newton and Copernicus changed the idea of reality from qualitative and teleological to quantitative and mechanical, and Einstein's relativity and quantum physics are revolutions that still puzzle traditional ontologies. On such ontological implications and their possible interpretations see, for example, two very different thinkers (Prini, 1988; Žižek, 2012 – and, in particular, chapter 14: The Ontology of Quantum Physics). Therefore, the ever recurring question is: how is it possible to reconcile the findings of science and of systematic philosophical reflection? And more specifically, in our case, how is it possible to reconcile the findings of neuroscience and philosophy?
With profound respect for Patricia Smith Churchland, I here discuss some of the methodological points of neurophilosophy presented by her, with which I profoundly disagree. Hopefully, by exploring briefly the background to these questions, a new light will also be shed on the foreground, namely on what Peter Singer said in the interview.

Three arguments against naturalism
Which monism?

First of all, Churchland says that neurosciences render a Cartesian-like mind/brain dualism implausible: «Since the weight of evidence indicates that mental processes actually are processes of the brain Descartes' problem

has disappeared. The classical mind/body problem has been replaced with a range of questions: what brain mechanisms explain learning, decision making, self-deception, and so on. The replacement for "the mind-body problem" is not a single problem; it is the vast research program of cognitive neuroscience» (Churchland, 2008a).
This, then, is my first argument. Half of the story is being missed here: if neurosciences make the mind as a separate entity (res cogitans) disappear, then they make matter understood as a brute, inertial entity (res extensa) disappear as well. Hegel might, unexpectedly, be recalled here. In the section on phrenology of The Phenomenology of Mind he writes the following:
1) «[…] that the existence of mind is a bone [daß das Sein des Geistes ein Knochen ist]» (Hegel 1807).
2) «[…] connection of higher and lower which, in the case of the living being, nature naïvely expresses when it combines the organ of its highest fulfillment, the organ of generation, with the organ of urination [Verknüpfung des Hohen und Niedrigen, welche an dem Lebendigen die Natur in der Verknüpfung des Organs seiner höchsten Vollendung, des Organs der Zeugung, – und des Organs des Pissens naiv ausdrückt]» (Hegel, 1807).
Such speculative (and not naturalistic) statements provide a philosophical account consistent with neurosciences, possibly even more than naturalism: the mind as a transcendent beyond, as a res cogitans, is not explained away by neurosciences, on the contrary it is incorporated into the brain. The Hegelian temptation here is to say that both brain and mind are sublated [aufgehoben] in a more concrete concept: a thinking extension and extended thought (extensio cogitans cogitatioque extensa).

Are there facts, interpretations, or both?

Another key point of this naturalism is the denial of *a priori* forms of argumentation. In the 1970s philosophers like W.V. Quine and P. Feyerabend «undermined the conventional wisdom that philosophy was an a priori discipline whose truths were accessible by non-empirical methods, and whose discovery supposedly laid the a priori foundation for any science» (Churchland, 2008b). In another passage Churchland describes what an a priori form of argumentation is like: «The dominant methodology of philosophy of mind and morals in the twentieth century was conceptual analysis.
Pilloried by philosophers of science as know-nothing philosophy, conceptual analysis starts with what introspection reveals about the allegedly unassailable truths of folk psychology. Then, via reflection and maybe a thought experiment, you figure out what must be true about the mind. A frankly a priori strategy, conceptual analysis ran up against a torrent of neuropsychological results that clashed with the "truths" of folk intuition» (Churchland, 2008a).
Let us make some distinctions:
a) *A priori* does not mean conceptual analysis in Churchland's sense: what she describes is basically just the analytical "vulgarized" a priori argumentation, very close to the mere presentation of one's opinion.
b) *A priori* means that some truths do not depend on facts or experience. And this is held to be false by naturalism. So:
I) If the claim of naturalism is that truths depend exclusively on scientific facts and experiences (experiments), that is evidently false.
II) If the claim of naturalism is that truths depend on facts and experience generally meant, this is true even for an Hegelian philosopher. But only as long as — and this is my second point — the obverse also is true: there are no facts and experience independent of truth(s); facts and experience are always already contained within a conceptual framework. Genuine a priori argumentation has many names in philosophy, from metaphysics (Aristotle) to critique (Kant) to speculative logic (Hegel, Jaspers) to eidetic reduction (Husserl), and it indicates the work on concepts, principles and methods of philosophical research.
To put the problem again in somewhat simplistic terms: if Quine denies a priori truths (Quine, 1960), we have to summon once more the ghost of Hegelianism and supplement Quine with Giovanni Gentile. Maybe the fundamental trait of Gentile's style of argumentation is that of reducing dichotomies to concrete unities and showing the primacy of the "I think", the pure activity of thinking. He would therefore argue: if there is no a priori as such, there is no a posteriori as such either (Gentile, 1924). Or, in even more simplistic terms: all truths depend on facts except Truth itself, which is somehow an innate concept and cannot be defined in a non-circular way: as G. Frege showed, the definition of Truth has to be true (Greimann, 2015).

Two sides of reduction

The last issue is that of reductionism. Churchland, in an illuminating passage, well worth quoting, writes: «Many contemporary dualists also shared a rhetorically convenient misunderstanding […] if a science reduces a macro phenomenon to a micro phenomenon, then the macro phenomenon is not real or "goes away" […]. The heart of the misunderstanding concerns the idiosyncratic notion of reduction, where it tends to be assumed that in science reductions make things disappear. This assumption is just confused. Famously, physics reduced visible light to electromagnetic radiation, but no one believes that light therefore ceased to be real or became scientifically unworthy. Temperature was reduced to mean molecular kinetic energy, but temperature did not disappear. Some beliefs about the nature of light and temperature did change, but the important point is this: reduction of a phenomenon traditionally means only that we have an explanation of the phenomenon […]. Given the aforementioned confusion about "reduction", the expression "the reduction of A by B" might usefully be replaced by the expression "the explanation of A by B"» (Churchland, 2007).
It is symptomatic that Churchland uses only scientific cases of reduction as examples. Indeed — and this is my third argument — if we reduce something within its own field we are actually explaining it (as in reducing a natural substance like sugar to its molecular components, say), otherwise we are explaining it away — in more classical terms we are operating a *metàbasis eis àllo ghènos*, a change into another kind of genus. A reduction of a natural phenomenon to its natural causes, within its own field, is actually a reduction as explanation (a); instead, reduction of, say, a religious phenomenon, or an economic or political phenomenon, to its (sup-

posed) natural causes, and therefore to another field, seems to constitute reductionism (b).
We can here recall another Hegelian thinker, Benedetto Croce: one of his main assumptions, clearly stated in many books and fairly convincing, is that the diversity of fields like aesthetics, philosophy, politics and morals is an irreducible diversity. We therefore have to use different conceptual frameworks to grasp each of these fields in order not to miss their proper significance (Croce, 1907; Bonetti, 1984).
Let us try with an experiment. I will quote a passage of Dostoevsky's Crime and Punishment and then re-write it reducing it to naturalistic terms.
«A minute later Sonia, too, came in with the candle, set down the candlestick and, completely disconcerted, stood before him inexpressibly agitated and apparently frightened by his unexpected visit. The colour rushed suddenly to her pale face and tears came into her eyes.… She felt sick and ashamed and happy, too.… Raskolnikov turned away quickly and sat on a chair by the table. He scanned the room in a rapid glance» (Dostoevsky, 2000).
And now the reduced version:
A minute later Sonia too was brought in by the muscles of her legs, with the candle; she set the candlestick down and, with her facial muscles moving rhythmically, stood before him in evident psychomotor agitation and with a region of her amygdala apparently stimulated by his unexpected visit. Her blood pressure and the pulse changed suddenly and her lacrimal glands began working… The area of her brain related with emotions was crossed by opposite stimuli… Raskolnikov turned away quickly and sat on a chair by the table. His eyes were detecting many electromagnetic radiations from the room.
It should be evident that in the reduced second version something is lost. This x is precisely the problem of reductionism (b), whereas in a genuine reduction (a) nothing should be missing.

Conclusions

After this digression, let us switch back from the background to the foreground, and Singer. Does it throw a new light on him? I am persuaded that my three arguments are also valid in his regard.
On the one hand, Singer's ethics is evidently consistent with its premises, simple and handy. But on the other, to cut a long story short (and maybe adding a touch of irony), his utilitarianism reduces ethics to calculation — evil to electricity and nervous stimuli.
We can accept this in the case of physical pain, but things become more complicated in that of a properly moral pain or symbolic pain (like the pain of someone whose life is shattered by, say, the end of a love affair) (see Milanesi and Nappi, 2009).
His claim for animal rights is serious and absolutely worthy of consideration, but its neurological foundation does not seem, to me, completely convincing so far. The monistic attempt to arrive at one principle of ethics is appropriate, but the principle seems to me the wrong one. Instead, his methodological monism prevents us from seeing the specificity of other degrees of reality, as in the case of religion.
Finally, my critique of reductionism might also remind us that the philosopher's task is primarily that of interpreting the world and must not be reduced to political activism as Singer seems to do. Marx's eleventh thesis on Feuerbach must be turned upside down here: "Philosophers have hitherto only tried to change the world in various ways; the point is to interpret it".

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Add-on perampanel and aggressive behaviour in severe drug-resistant focal epilepsies

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Summary

This study aimed to investigate the incidence of aggressiveness in patients with severe drug-refractory focal epilepsy (DRE) who started perampanel (PER) as add-on treatment, and to identify possible predisposing factors.
Data on 49 consecutive patients with severe DRE who initiated PER were retrospectively collected. Twelve of the 49 patients experienced aggressiveness as adverse event related to PER treatment, one third of them on low (2-4 mg/day) PER dosages. PER was discontinued in 10/12 patients because of aggressive behaviors. Aggressiveness could appear after several months or even more than one year of PER treatment. One third of patients with PER-related aggressiveness had intellectual disabilities and 5/12 patients took levetiracetam as a concomitant antiepileptic drug.
Our study suggests that the occurrence of aggressive behaviors in patients with severe DRE is not uncommon during PER treatment and that it may occur after months or even years of treatment with a stable dosage, requiring PER discontinuation in the great majority of patients.

KEY WORDS: adverse events, aggressiveness, focal epilepsy, perampanel, psychiatric side effects.

Introduction

Perampanel (PER) is a selective non-competitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonist that is employed as an adjunctive therapy for focal seizures with or without secondarily generalized seizures in patients with epilepsy aged >12 years. The efficacy and tolerability of PER have been assessed in a clinical trial program, which included three randomized, double-blind, placebo-controlled phase III studies in patients suffering from drug-resistant focal seizures (Krauss et al., 2012; French et al., 2012, 2013) and one extension study (Krauss et al., 2014). PER carries a warning about the risk of serious neuropsychiatric adverse events (AEs), including irritability, aggression and anger (European Medicines Agency, 2017; Food and Drug Administration, 2017). Indeed, an analysis of pooled safety data from these three phase III studies suggests that psychiatric AEs are associated with use of PER (Ettinger et al., 2015). In addition, several real-life observational studies have found behavioral disturbances to be a major side effect both in adulthood and pediatric age (Coyle et al., 2014; Biró et al., 2015; Juhl and Rubboli, 2016) reporting higher rates of occurrence than those found in pre-marketing clinical trials. These findings have been challenged by a recent controlled study in adolescents which showed that PER was not associated with clinically relevant behavioral adverse events, but concluded that more data are needed to determine whether PER can be specifically associated with aggressive behavior (Lagae et al., 2016).
In this real-life observational study we retrospectively reviewed our series of patients who started PER as an add-on treatment. Our aims were to investigate the incidence of aggressiveness after PER introduction and possibly to identify any predisposing factors.

Materials and methods

All consecutive patients with severe drug-refractory focal epilepsy (DRE) who started PER as add-on treatment from November 2012 to December 2015 were retrospectively analyzed. The series includes 22 previously reported patients (Juhl and Rubboli, 2016). Epilepsy type was determined by clinical history and by EEG/video-EEG investigations. Seizures were classified as simple partial, complex partial, or secondarily generalized tonic-clonic. Seizure frequency ranged from daily to monthly. The etiology was: mesial temporal sclerosis (7 patients), brain tumor (6), neonatal infarction (4), cortical dysplasia (4), heterotopia (2), stroke (2), meningitis (2), herpes encephalitis (1), meningioma (1), cavernous angioma (1), intrauterine cytomegalovirus infection (1), head trauma (1), unknown (17). Eleven patients had intellectual disabilities (IDs) of varying severity. The mean PER daily dose was 6.6 mg (range: 2-12 mg). PER was initiated at a dose of 2 mg once daily at bedtime and it was up-titrated by 2 mg per week or 2 mg every four weeks, according to medical needs, concomitant medications and the occurrence of side effects. Clinical assessment after PER introduction was performed during outpatient clinical consultations (usually every 3-6 months) and reported in the medical records. Information on worsening of AEs, including neuropsychiatric AEs, after PER initiation was retrieved by reviewing the medical charts and, in most of the cases, by contacting the patients and their relatives. The appearance or worsening of aggressive behavior was defined as the appearance or worsening of verbal or behavioral aggressive manifestations, including physical aggression, as reported by the patient or his/her relatives. In partic-

Table I - Patient characteristics.

Pts	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5
Gender, age (years)	F, 50	F, 32	M, 32	F, 59	F, 49
Age at epilepsy onset (years)	14	1	1	2	9
Etiology	Unknown	Unknown	Unknown	Left MTS	Unknown
Intellectual disabilities	No	Yes	Yes	No	No
Psychiatric comorbidity	Depression	No	No	Anxiety, obsessive-compulsive disorder	No
Seizure types	CPSs	CPSs, sGTCSs	CPSs, sGTCSs	CPSs	CPSs
Seizure frequency before PER	8-11/mth	5-8/mth	11-17/month	4/month	Daily/weekly seizures
Concomitant AEDs Maximum PER dosage/day	LEV, LTG, PRG, CLB 6 mg	TPM, SLT, VPA (+VNS) 2 mg	TPM, VPA, SLT, CLB 8 mg	LEV, CNZ, CBZ 4 mg	LTG, LCM, CLB, RTG (+VNS) 8 mg
Duration of PER treatment	28 months (ongoing)	2 months	12 months	7 months	26 months (ongoing)
Concomitant treatment changes during PER treatment	None	None	None	None	Withdrawal of RTG
Seizure frequency during PER treatment	<50% reduction (seizures were milder)	Unchanged	>50% reduction	>50% reduction	<50% reduction (seizures were milder)
Side effects	Aggressiveness, "bad" mood tiredness, dizziness, concentration difficulties	Aggressiveness, mood swings, tiredness	Aggressiveness, tiredness	Aggressiveness, "bad" mood, difficulty in finding words	Aggressiveness, mood swings
Management of aggressiveness	Reduction of PER dosage (to 4 mg/day)	PER withdrawal	PER withdrawal	PER withdrawal	Reduction of PER dosage (to 4 mg/day)

Abbreviations: F=female; M=male; MTS=mesial temporal sclerosis; CMV= cytomegalovirus; CPSs=complex partial seizures; SPSs=simple partial seizures; sGTCs=secondarily generalized tonic-clonic seizures; LEV=levetiracetam; LTG=lamotrigine; PRG=pregabalin; CLB=clobazam; SLT=sulthiame;

ular, hostile, injurious, angry reactions towards others (including screaming and arguing) were considered to constitute verbal aggression. The patients and their relatives were asked specifically about behaviors (most of the time the relatives reported them spontaneously without being asked) and whether they were first noticed or became more pronounced after PER initiation. Causes of PER discontinuation were specified in the medical records. In the group of patients who presented aggressiveness, we assessed effectiveness by comparing the overall frequency of all seizure types between baseline (the four weeks before PER initiation) and the last three

Pt.6	Pt.7	Pt 8	Pt 9	Pt 10	Pt 11	Pt 12
F, 43	M, 67	F, 51	F, 48	M, 25	F, 30	M, 42
25	27	20	43	6 months	Since birth	12
Cortical dysplasia	Brain tumor (glioma)	Cavernous angioma	Unknown	CMV infection	stroke	Unknown
No	No	No	No	Yes	Yes	No
No	No	No	No	No	No	No
CPSs	CPSs, sGTCSs	SPSs, sGTCs	SPSs, sGTCs	sGTCs	SPSs, sGTCs	CPSs, sGTCs
5-8/month	2-3/month	1/month	2-3/month	4/month	1-3/month	Daily/weekly seizures
LTG, RTG, CLB (+VNS)	LCM, VPA, CLB (+VNS)	LEV, ZNS	LTG	LEV, VPA	VPA, LEV, LCM, TPM	CBZ, CLB, LCM
8 mg	4 mg	4 mg	8 mg	8 mg	6 mg	6 mg
6 months	5 months	24 months	18 months	32 months	10 months	7 months
Withdrawal of RTG	Withdrawal of VPA	Withdrawal of ZNS	None	None	Withdrawal of LCM	None
Unchanged	Unchanged	Seizure freedom	Unchanged (seizures were milder)	>50% reduction	Unchanged	Unchanged
Aggressiveness, "bad" mood	Aggressiveness	Aggressiveness, "bad mood" concentration difficulties, tiredness	Aggressiveness "bad" mood, concentration difficulties	Aggressiveness	Aggressiveness, irascibility, tiredness	Aggressiveness, headache, tiredness, double vision
PER withdrawal	PER withdrawal	PER withdrawal	PER reduction then withdrawal	PER reduction then withdrawal	PER withdrawal	PER withdrawal

TPM=topiramate; VPA=valproic acid; CNZ=clonazepam; CBZ=carbamazepine; LCM=lacosamide; RTG=retigabine; ZNS=zonisamide; PER=perampanel; VNS=vagal nerve stimulator

months, as reported at the last outpatient clinic consultation. The minimum follow-up after PER initiation, to assess effectiveness, was six months. Responders were defined as those patients whose seizure frequency was reduced by at least 50%. Aggravation of seizures was defined as an at least 50% increase in seizure frequency.

Results

Forty-nine consecutive patients started PER as an add-on treatment in the period from November 2012 to December 2015. Twelve (M/F=4/8) of the 49 patients experienced aggressiveness as a PER treatment-related

AE. Clinical data of the patients are shown in Table I. Their mean age was 44 years (range 25-67 years) and their mean age at epilepsy onset was 12.8 years (range: birth-43 years). The mean duration of epilepsy was 31.3 years; range: 5-57 years. In 11 of the 12 patients the seizure frequency at the baseline varied from daily seizures to 17 seizures per month; only one patient (#8) had monthly seizures. The mean number of antiepileptic drugs (AEDs) per patient at initiation of PER was three (range 1-4); 3 patients also had vagal nerve stimulation. In 5 patients, one concomitant AED was withdrawn during PER treatment (Table I). The mean daily dose of PER was 6 mg (range: 2-8 mg). The titration rate was 2 mg/2 weeks in 2 patients and 2 mg/4 weeks in 9 patients (1 patient took only 2 mg/day as maximum dosage before withdrawal). Four of the 12 patients had IDs. Psychiatric comorbidity was observed in patient #1 (depression) and in patient #4 (obsessive-compulsive disorder and anxiety). No previous history of psychiatric or behavioral disturbances was reported in the other patients.

Aggressiveness referred to a spectrum of manifestations that could range from angry, violent, hostile verbal reactions to overt physical aggressiveness (one patient repeatedly hit his parents for trivial reasons). All the patients and their relatives reported the appearance of these behaviors after the introduction or up-titration of PER. Other behavioral or psychiatric AEs were a "bad" mood (5 patients), mood swings (two patients), and irascibility (1 patient). In 10 patients (10/12 of the subgroup of patients with aggressiveness, 10/49 of the whole analyzed cohort), the aggressive manifestations were considered intolerable either by the patient or by his/her family and led to discontinuation of PER, even in subjects showing a remarkable reduction of seizure frequency. In fact, one third of patients achieved a >50% seizure reduction, including 1 patient (#8) who became seizure free. Four of the 12 aggressive patients exhibited aggressiveness at low PER dosages (2 mg in one, 4 mg in three). PER tapering was performed, reducing the dosage by 2 mg every one-three weeks. After PER withdrawal, behavior greatly improved or normalized in all the patients, as reported by the patients themselves and their relatives. In 2 patients (#1 and #5) aggressiveness improved by reducing the dosage by 2 and 4 mg, respectively, therefore PER was not discontinued. These 2 patients have now been taking PER for 28 and 26 months respectively; in both, the seizure reduction is <50%, but seizures are reported as milder.

The duration of PER treatment ranged from 2 to 32 months (mean: 14.7 months). Interestingly, appearance of aggressive behaviors could occur after several months of stable and well tolerated PER treatment. In fact, 4 out of 10 patients (#3, #8, #9, #10) had taken the drug for at least 12 months. Patient #8 had achieved seizure freedom with a low dose (4 mg) of PER; she developed aggressive behaviors about 20 months after PER initiation, which led to PER discontinuation after 24 months of treatment. On the contrary, in 2 patients (#2 and #7), intolerable aggressiveness appeared shortly after PER initiation, resulting in PER discontinuation after two and five months of treatment, respectively.

The AEDs most frequently associated with PER were: clobazam in 6/12 patients, levetiracetam in 5/12, valproic acid in 5/12, lacosamide in 4/12, and topiramate in 3/12, in various combinations.

Discussion

The most common AEs of PER reported in pre-marketing clinical trials were dizziness, somnolence and headache (Steinhoff et al., 2013). Psychiatric AEs were described in only a small proportion of patients, and the rate of occurrence increased at higher PER dosages. In particular aggression was reported in only 3.1% of patients on PER 12 mg/day as compared to 0.5% of patients taking placebo (Steinhoff et al., 2013). With regard to adolescent patients, further analysis of the phase III PER studies and a recent randomized study have shown that aggressive behavior occurred in about 8% of cases (Rosenfeld et al., 2015).

Our observational study in a cohort of patients with severe DRE revealed PER-related aggressiveness in about a quarter (12/49) of patients, a higher incidence than those reported in pre-marketing studies. Our findings are similar to those published by Coyle et al. (2014) in adults, and by Biró et al. (2015) in children and adolescents, who reported psychiatric AEs, including mood swings, irritability and aggression, in 25 and 24% of patients, respectively. On the other hand, the present findings are discordant with other real-life observational studies which reported the appearance of irritability and aggression in only about 2% of patients (Steinhoff et al., 2014). This discrepancy might depend on the characteristics of our study group, which was a highly selected cohort of patients with severe DRE, and on our longer observation period after PER initiation, which allowed us to detect the appearance of aggressiveness after several months or even after more than one year of stable PER treatment, at variance with previous preclinical and observational studies that included more heterogeneous groups of epilepsy patients and had shorter follow-ups. The interpretation that longer follow-ups might be associated with an increased rate of aggressive behaviors is further supported by the observation that in adolescents who continued PER in the extension study, aggression occurred in up to 18% of patients (Rosenfeld et al., 2015).

In our study we could not confirm that the occurrence of aggressive behavior was related to high PER dosages, as suggested by pre-marketing clinical trials; indeed the maximum dosage of PER was 2-4 mg/day in 4 of our patients and 6 mg/day in a further three. Other observational studies also failed to detect a correlation between occurrence of side effects and PER dosage (Steinhoff et al., 2014; Coyle et al., 2014). In addition, we did not find any correlation between occurrence of aggressiveness and titration rate, since in most of our patients, PER was increased at the slowest rate of 2 mg every four weeks. Our results further document the effectiveness of PER in reducing seizure frequency in patients with severe DRE, since a seizure reduction >50% at six months of follow-up was observed in one third of the patients (including one seizure-free patient), and two additional patients reported a reduction of seizure frequency (albeit < 50%) and seizure intensity. However, in spite of the seizure improvement, the intensity of the aggressive manifestations, in particular when associated with mood changes, were considered, by 10/12 patients and their relatives, sufficiently intolerable and worrisome to warrant PER discontinuation. PER withdrawal was followed by resolution of or a remarkable decrease in aggressiveness. In

the remaining patients, reduction of the PER dosage was effective in improving the aggressive behavior, and allowed the PER treatment to be continued.

More than one third of the patients in our series affected by ID developed PER-related aggressive behavior, which required discontinuation of the treatment in all of them. This finding is in agreement with the findings of recent studies by Snoeijen-Schouwenaars et al. (2017) and Huber and Schmid (2017) in patients with epilepsy and IDs who reported behavioral AEs, including, aggression, irritability mood changes, in about 40 and 50% of subjects, respectively. These observations should alert us to the possibility that PER may be not tolerated in a non-negligible proportion of epilepsy patients with IDs. On the contrary, psychiatric comorbidity was observed only in 2 of our patients with PER-related aggressiveness, suggesting that it may not play a role in the development of behavioral AEs.

With regard to the possibility that aggressiveness could result from the combination of PER with other drugs, the limited number and the heterogeneity of the polytherapies in our cohort prevent us from drawing clear-cut conclusions. In previous studies (Glauser et al., 2016; Snoijen-Schouwenaars et al., 2017), polypharmacy did not predict an increased probability of occurrence of side effects, including psychiatric AEs. In our study, 5/12 patients who developed aggressiveness took levetiracetam, a drug which has been reported to be associated with aggressive behavior (Dinkelacher et al., 2003; Wieshmann and Baker, 2013). In addition, pharmacodynamic interactions between levetiracetam and PER have been suggested (Patsalos et al., 2015). Therefore, we cannot exclude that the combination of these two drugs may reduce the tolerability of PER, increasing the risks of behavioral and psychiatric AEs. Finally, the possibility that in our patients the occurrence of aggressiveness might be related to modifications of treatments with concomitant AEDs seems unlikely since only a minority of patients changed their AED regimen (withdrawing one drug) during PER treatment.

Previous studies have shown that some patients may develop psychiatric AEs during treatment with different drugs with distinct mechanisms of action, suggesting that these patients might be prone to develop psychiatric AEs when taking any AED (Mula et al., 2007). However, this possibility does not seem to apply to our patients since only 2 of them had a psychiatric comorbidity and none of the others had ever reported psychiatric disorders during previous AED regimens. In addition, they returned to their baseline behavior as soon as PER was reduced or interrupted.

We are aware that the retrospective design of our study inevitably means that we may have missed or misinterpreted some data, or neglected some confounding factors. However, the data collection was based not only on retrieval of information from medical charts, but also on questioning, specifically for this study, of the majority of the patients and their relatives about the occurrence and type of aggressive manifestations, and their relationships with the initiation of PER. In addition, we acknowledge that the size of our cohort is limited and that it is composed of a highly selected group of patients with severe DRE referred to a tertiary center, and this has to be taken into consideration before extending our findings to the general population of patients with epilepsy.

In conclusion, our study suggests that in patients with severe DRE the occurrence of aggressive behaviors may be not uncommon during PER treatment, and that these may appear after months or even years of stable dosage, requiring PER discontinuation in the great majority of patients, even in the presence of a remarkable reduction in seizure frequency. In addition, coexistence of IDs and association of PER with levetiracetam might increase the probability of developing aggressiveness, however, further studies are warranted to confirm these latter findings. Finally, our data indicate that patients and their relatives should be counselled on the risk of psychiatric AEs, including aggressiveness, when PER is initiated.

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