

Review Article

PDE5 Inhibitors, Erectile Dysfunction and beyond: How, Sometimes, Indications are the Consequences of Marketing Strategies and/or Serendipity

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Abstract

Phosphodiesterase inhibitors (PDE5i) have an established role in the treatment of erectile dysfunction (ED) and pulmonary arterial hypertension (PAH) but, at the same time, they represent a paradigmatic example of a class of drugs, originally tested for a clinical indication, shifted to another one, for the unexpected emergence of strong evidences opening towards a new market, at that time still to be defined, but with an enormous potential. Sildenafil, the primer of PDE5i drugs patented in 1996, was designed and thought as anti-hypertensive/anginal, early relocated for ED and approved for this in 1998 despite emerging evidences of a further possible use, albeit numerically limited, in PAH. The apparent lack of interest in other fields of application continue at least until 2004 when, possibly, due to the upcoming of 2 new PDE5i on the market, the request for PAH, supported by a trial, was finally submitted and obtained by FDA in 2005. It is noteworthy that in medicine, when a relevant cellular mechanism is identified and targeted with a new drug, the results are not always predictable and/or are in agreement with the interests of the market but serendipity can help. Thus development/marketing of drugs is a multifactorial phenomenon that includes, also, potential/effectiveness of the molecules, beliefs/curiosity of the researchers, doctor/patient expectations, and, first of all, the economical interest related to their economic exploitation. In this review we wanted to explore the potentials, if any, of PDE5i beyond ED, by searching the literature for off-label applications.

ABBREVIATIONS

cAMP: adenosine 3',5'-cyclic monophosphate; CAD : Coronary Artery Disease; Ca²⁺: Calcium; ED: Endothelial; FDA: Food and Drug Administration; cGMP: Guanosine 3',5'-cyclic monophosphate; GTP: Guanosine 5' Triphosphate; HF: Heart Failure; NO: Nitric Oxide; PAH: Pulmonary Arterial Hypertension; PDEs: Cyclic Nucleotide Phosphodiesterase; PDE1i: Phosphodiesterase Inhibitors; PDE3i: Phosphodiesterase Inhibitors; PDE5i: Phosphodiesterase Inhibitors; PKG: Protein Kinase cGMP dependent; QoL: Quality-of-Life; SUPER-1: SUPER-1 trial (Sildenafil Use in Pulmonary hyper- tension)

INTRODUCTION

Cyclic nucleotide phosphodiesterase (PDEs) superfamily is almost ubiquitously distributed in mammalian tissues [1] and

this because they play an essential role in hydrolyzing Adenosine 3',5'-cyclic monophosphate (cAMP) and guanosine 3',5'-cyclic monophosphate (cGMP) to the inactive metabolites AMP and GMP. Together with intracellular calcium and Inositol triphosphate -that induces the release of calcium from intracellular stores- PDEs, through the hydrolysis of cAMP and cGMP, modulate intracellular signal transduction. There are most than fourteenth different isoforms of PDEs, some of them are selective for cAMP and other for cGMP, and this ensures a specific distribution at different cellular and sub-cellular levels and regulation of several functions. Thus we can find these enzymes in human platelets, vascular and bronchial smooth muscle, renal tubules [2], heart, brain, pancreas, bladder, urethra, penis, ovary [3] and retina [4]. The pattern of tissue distribution of PDEs and their role in intracellular signaling support the general interest toward the development of specific inhibitors able to prolong or enhance

the effects of physiological or counteract pathological processes mediated by cAMP or cGMP by inhibition of their degradation. After a long period of research and development, started from the 1970s, PDEi having an established role are now PDE1i, PDE3i and PDE5i that is, undoubtedly, the most successful. It should be said that there are at least two non-selective PDEi that should be recalled, namely papaverin and teofillin, whose clinical use is to contrast the muscle contraction in gastrointestinal tract and bronchial airways. Among the others PDEi, Nimodipine, formally an L-type Ca^{2+} channel antagonist that also inhibits PDE1 activity, was originally developed for high blood pressure but it has shown potentials in the prevention of vasospasm caused by subarachnoid hemorrhage [5]. Milrinon and Amrinon are PDE3 selective inhibitors, they prevent the degradation of cAMP thus they are used for their inotropic effect in heart failure (HF) solely in emergency settings [6,7].

Finally PDE5i that are object of this review, by inhibiting PDE5 they increase intracellular cGMP levels decreasing intracellular calcium levels, thereby promoting relaxation of smooth muscle cells and other calcium-dependent processes. As we have already said PDE5i, starting from Sildenafil, the primer of the class, have gained an established role in the treatment of erectile dysfunction (ED) and pulmonary arterial hypertension (PAH) [8]. The mechanisms of action of PDE5i on the cGMP pathway are summarized for convenience in (Figure 1).

Aim of the review

It is beyond this review to celebrate the “myth of the origins” and the established properties of the founder of PDE5i class, for which we refer to the excellent case history article [9]; nonetheless, the evidences on PDE functions and the relevant role of PDEi in the modulation of intracellular signaling, clashes with the fact that only few PDEi are currently used for a known therapeutic indications and, despite the ubiquity of PDE, these indications are numerically limited.

Thus we aimed this review to provide a brief historical perspective on the development of the PDE5 inhibitors and current use focusing on the unrealized potential, if any, of this class by retrieving the literature (MedLine) and reporting the number of papers, grouped by *scope of use* of PDE5i, inside and outside the commercial license (off-label applications). For the search strategy, we used extensively the keyword phosphodiesterase 5 inhibitors and its acronym to include whole items without setting “limits” for *article type, availability of text, date of publication, and the species studied*.

We are aware that the results we report, in terms of matching papers, are raw data, including both potential and reality about the use of PDE5i since the scope of use cited may be in, many cases, merely speculative.

Development of a new anti-hypertensive/anginal drug

The history of Sildenafil, the primer of PDE5i, started about 30 years ago in Pfizer Central Research’s laboratories; some researchers found that the inhibition of the enzyme Phosphodiesterase 5, that is in vascular smooth muscles, reduce the vascular tone and platelet aggregation. The first commercial

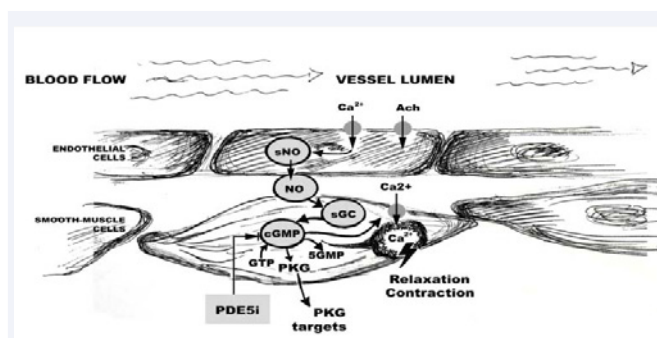


Figure 1 Cholinergic system determine the production of Nitric Oxide (NO) in response to stimulation a Ca^{2+} pathway in endothelial cells. Ca^{2+} once released activates NO synthesis that diffuses across the smooth-muscle cell and binds to guanylate cyclase (sGC). Thus the synthesis of guanosine 3',5'-cyclic monophosphate (cGMP) is catalyzed by sGC from guanosine 5' triphosphate (GTP). Then cGMP activates a protein kinase cGMP dependent (PKG) which stimulates the uptake of Ca^{2+} by the endoplasmic reticulum of the muscle cell. The reduced levels of cytoplasmic calcium cause the muscle cell to relax.

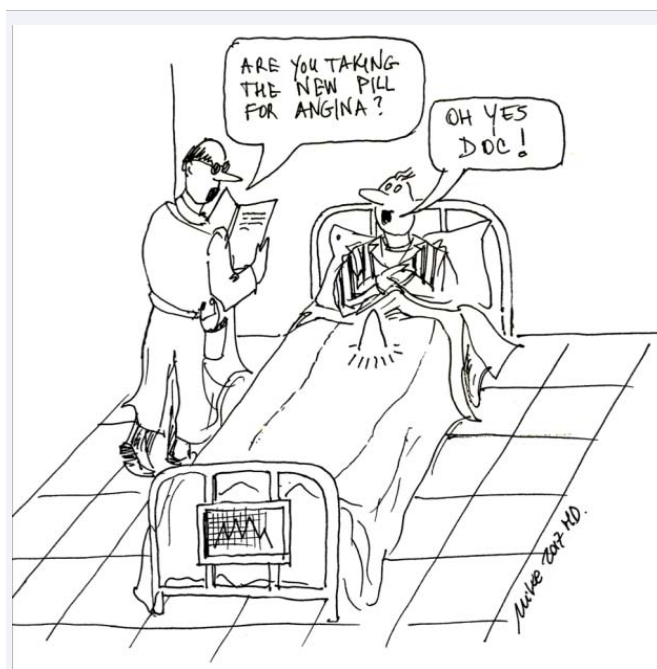


Figure 2 A joke lampooning the unexpected developments of the experimentation with Sildenafil.

inhibitor of PDE5 was indeed Sildenafil (UK-92,480), synthesized in the 1980s as a potential treatment for arterial hypertension and angina pectoris. The hypothesis was that inhibition of PDE5, in heart and blood vessels, could lead to significant coronary vasodilation with benefit for patients with coronary artery disease (CAD) [10]. After few years of unsatisfactory experimentations, some of the patients recruited in this study report a pleasant side effect consisting in penile erection (Figure 2). This side effect that was unexpected, potentially useful, able to revolutionize the use of this drug and extend to a potentially large number of subjects, led to the closure of its development as anti-anginal. Indeed Sildenafil in patients with CAD demonstrated

a modest cardiovascular effect, instead the action of PDE5i on penile erection in men, determined its fundamental role in the therapy of the erectile dysfunction (ED).

An unexpected effect introduces a new indication

Sildenafil, patented in 1996, was relocated for ED and approved for this in 1998 by Food and Drug Administration (FDA). The marketing of a drug designed for a new clinical indication such as ED, inevitably contributes to the arise of a clinical problem that was, before, almost neglected following a phenomenon known as “disease mongering” [11], a problem that is not object of this review. Indeed ED is common in middle-aged and older men, though not subject to cardiovascular or psychiatric problems. It should be remembered that there are several organic causes for ED including hypogonadism, hyperprolactinemia, pelvic artery diseases and various causes of neuropathy; furthermore antipsychotics, antidepressants or antihypertensive drugs may cause ED as side effect. Often a non-organic cause is identified and the problem is the result of a combination of organic and psychological factors, such as sexual performance anxiety, which can lead to a vicious circle [12]. In this quite complex interplay between organic and non-organic causes of ED, the availability of a new class of drugs, with a good safety profile and modest side effects, contributed to make PDE5i the first choice for ED and a worldwide commercial success. The most common side effects are headaches, flushing, and epistaxis and these concerned with high tissue concentrations of PDE5. The feared risk of Sildenafil to cause orthostatic hypotension in subjects with CAD is more relate with the interaction of PDE5 with multi-drug antihypertensive therapy. Indeed Sildenafil is a mixed vasodilator with a preferential action on veins [13] therefore the combination with nitrates could lead to severe vasodilation and hypotension. Generally Sildenafil is hemo dynamically safer even when added on top of vasoactive treatment [14]. Moreover PDE5i has a weak inhibition of PDE6 that is found especially in the retina, thus, it is reported a transient blurred vision or difficult in discriminating blue-green colors or light sensitivity in course of Sildenafil therapy [15]. Eyesight disorder such as non-arteritic ischemic optic neuropathy and cilio-retinal artery occlusion are signaled in a limited number of case reports [4]. While no proven vision-threatening effects were apparent in meta-analyses, minor visual effects occur in 3-11% of users and are, either, transient

or reversible [16]. The commercial success of the first patented molecule prompted the development of other PDE5i: Vardenafil, Tadalafil, Avanafil. A summary of dosage, pharmacokinetic and pharmacodynamic features are reported in (Table 1). These drugs received the Food and Drug Administration (FDA) approval for the treatment of ED; Sildenafil and Tadalafil were approved for the treatment of PAH [17]. Indeed, in the very last years, other PDE5i have been synthesized but they will not be mentioned in this review.

Beyond erectile dysfunction: pulmonary arterial hypertension

Beyond ED, emerging evidences of a possible use of Sildenafil, albeit numerically limited, in PAH began to circulate in the cardiological community at the beginning of the second millennium. When the first case report demonstrating a clinical benefit of Sildenafil in PAH was published in 2000 [18], there was an apparent lack of interest of the producer in other fields of application, at least, until the funding of the SUPER-1 trial (Sildenafil Use in PULmonary hyper- tension) that started to enroll patients with PAH, randomized to receive Sildenafil or placebo, in 2002 [19]. Before the results of the SUPER-1 were published, a randomized, placebo-controlled, double-blind, crossover study, started independently on this indication, had already been published in 2004 [20]. Thus urged, possibly, by the upcoming of 2 new PDE5i on the market and by general consensus on the utility of PDE5i in PAH, the request for this indication was submitted by the company owner of the molecule -with the endorsement of the results of the SUPER-1, finally published in The New England- and thus obtained by FDA in 2005. Indeed, as we have already said, among all the upcoming PDE5i, only Tadalafil has followed the same path of Sildenafil and obtained the FDA approval for PAH in 2009 [21]; on the same indication Vardenafil is now completing a clinical trial.

Unexpressed potentialities in other fields

The safety and high tolerability of PDE5i make them attractive drugs to investigate further physiological functions of PDE5. In recent years extensive, but very heterogeneous, information has been published in this field. A number of other potential indications are currently in various phases of preclinical research and development. By searching MedLine we have retrieved

	Sildenafil	Tadalafil	Vardenafil	Avanafil
Available doses (mg)	25-50-100	5-10-20	2.5-5-10-20	50-100-200
Effectiveness	60 min	15-30 min	30 min	15-30 min
Lasting (hours)	4-8 h	24-36 h	2-8 h	1-6 h
Food interaction	high-fat	Not significant	high-fat	Not significant
Alcohol interaction	None	None	None	None
Active metabolites	N-desmethylation	None	Desmethylation	Methylation, glucuronidation
Cytochrome P isoenzymes	3A4, 2C9, 2C19 and 2D6	3A4	3A4, 3A5, 2C9	3A4,2C
Excretion	77-88% feces; minor in urine	70% feces; 30% urine	91-95% feces; minor in urine	62% in feces; 21% urine

3701 papers on PDE5i; among them the main uses have been grouped into five categories, according to standard nosology, and reported by relevance: *a- Urological disease and alterations in sexual function and reproduction; b- Cardiovascular diseases and endothelial dysfunction; c- Central nervous system disorders; d- cancer, in e- other uses in which we have included recreational use, sports and jet lag.*

In Table (2) the results are summarized reporting the absolute numbers of matching documents.

Urological disease and alterations in sexual function and reproduction: This group is the most numerous since it includes the main approved indication for PDE5i; we have counted 1966 papers representing more than 53% of the total.

Among them, ED represents alone more than 49% of the total since others uses/indications are, indeed, a minority which stands on 4%; these uses are almost off-label and none of them have been studied in a clinical trial. Actually the only use of PDE5i beyond ED, supported by the American Urological Association, without strong evidences, is as alternative treatment, in combination therapy with alpha adrenergic antagonists, for the treatment of moderate to severe symptoms of benign prostatic hyperplasia [22].

Cardiovascular diseases and endothelial dysfunction: Numerically this group ranks second, including 1597 published papers, representing more than 43% of the total. Not surprisingly

PAH, the secondary approved indication for PDE5i, alone accounts 1050 papers that are more than 28% of the total. This possibly because PDE5i were firstly developed as anti-hypertensive/anginal and several studies were conducted in such therapeutical hypothesis. Furthermore, to treat endothelial dysfunction, that is at a major crossroads in cardiovascular pathophysiology, still make sense even if the optimism generated by pioneering studies in such field have not been confirmed beyond PAH.

Among the factors mediating cardiovascular disease and metabolic disorders that are, possibly, linked to PDE5 activity [23], cytokines and chemokines are a good candidate, they are small redundant proteins that, indeed, play an essential role in cell signaling by exhibiting a complex pattern of activation [24] that results in the reporting and management of cellular damage by modulating inflammation processes. Cardiovascular and metabolic diseases, mainly if a remodeling process is in fact, often exhibits pro-inflammatory cytokines, in such respect a possible role of PDE5i as a specific modulator of the inflammatory response, has been demonstrated in diabetic cardiomyopathy [25]. This possible effect could, also, support the favorable data observed in HF. The first data about the use of Sildenafil in patients with HF, preserved ejection fraction (HFpEF) and PAH have been published previously demonstrating that in the treated group a significant favorable reduction of alveolar-capillary membrane resistance, diminished pulmonary vascular tone, improved aerobic and ventilatory efficiency which lasted one year [26]. Unfortunately a subsequent randomized trial failed to demonstrate any significant differences between the two groups in the combined primary end points that were, indeed, many: change in peak oxygen consumption at 24 weeks, cardiovascular or renal hospitalization, pulmonary artery pressures, or quality-of-life (QoL) base on Minnesota Questionnaire [27]. Despite these results, it should be remembered that almost 80% of HFpEF patients already have PAH and the echocardiographic estimation of pulmonary pressures could help to definite the clinical prognosis [28]. Thus, after a comprehensive evaluation of the patients with HFpEF, the presence of PAH may still justify the use of PDE5i. Since this is still an active field of research, a new, randomized, placebo-controlled study failed to demonstrate that Sildenafil treatment could improve cardiovascular structure and function, cardiopulmonary exercise tests, or health-related QoL health measurements, however, the same authors suggest that the treatment period was limited to observe significant cardiac effects [29].

Central nervous system disorders: Numerically the papers in this group represent an absolute minority since we have found only 47 papers representing the 1.3% of the total. All the uses reported are, indeed, off-label; Sildenafil, Vardenafil, and Tadalafil has been shown to ameliorate the cognitive function and, possibly, to enhance synaptic plasticity [30-32] suggesting a possible role in Alzheimer's disease [33].

Cancer: Since PDE5 is expressed in different cancers, the prospect of a possible application of PDE5i, although controversial in some respects, is still attractive. The studies aimed at this scope represent only a minority of published papers; we have found only 10 papers, that is to say about the 0.3% of the total. The studies retrieved are all pre-clinical, the main effect of PDE5i

Table 2: References retrieved from MedLine quoting the use of PDE5i for a specific application/indication.

Use/indication [obtained from keywords]	Retrieved n*	vs Total %
Erectile dysfunction †	1836	49.61%
Pulmonary Hypertension †	1050	28.37%
Heart Failure	248	6.70%
diabetic peripheral neuropathy	220	5.94%
Female Sexual Dysfunction	65	1.76%
Raynaud's phenomenon ‡	46	1.24%
Stroke	31	0.84%
Sports	28	0.76%
Premature ejaculation	27	0.73%
Recreational use	24	0.65%
Preeclampsia	22	0.59%
Priapism	17	0.46%
Learning and memory	16	0.43%
Overactive Bladder and Incontinence	15	0.41%
Resistant Hypertension	11	0.30%
Cancer	10	0.27%
high-altitude Pulmonary edema	9	0.24%
Peripheral artery disease	8	0.22%
Peyronie's disease	8	0.16%
Benign Prostate Syndrome/Lower Urinary Tract Symptoms BPS/LUTS ‡	5	0.14%
high-altitude Pulmonary hypertension	5	0.14%
Jet lag	2	0.05%

† Drugs approved for the corresponding use; ‡ General consensus for the use, not yet approved by FDA.

in selected carcinomas, such as breast, colon, bladder and lung, was a reduction in the tumor volume which mechanism seems to be linked to a pro-apoptotic effect and to the inhibition of cellular proliferation and angiogenesis [34]. A further possible effect was the enhancement of the effects of chemotherapy in brain tumor models [35] and prostate cancer. A possible role in the treatment of malignancies of the hematopoietic and lymphoid tissues, with particular reference to B-Chronic lymphocytic leukemia, has been demonstrated in vitro studies [36]. Nonetheless in selected cancers such as brain ones and melanomas, an inverse correlation between PDE5 levels and invasiveness was reported [37].

Other uses: In *other uses* we have grouped the papers retrieved in which we have found, as uses, recreational, sport and jet lag one. They represent an absolute minority of the total, accounting 45 published papers, about the 1.2% of the total. However, it should be said that the recreational use, ranking a minority of published articles (24 papers; 0.6% of the total) has, on the contrary, a huge popular success since a survey published in J Sex Med reports that about 21% of healthy men, aged 18-30 years, have used PDE5i as a recreational drug without medical control [38].

Although the papers supporting off-label uses of PDE5i are indeed a minority, it is impossible to say that Sildenafil (and other similar drugs), are always used inside the commercial license and following standard medical criteria or control.

In Figure (3) are visualized minor uses of PDE5i.

DISCUSSION AND CONCLUSION

Notwithstanding the huge of paper celebrating the effects of PDE5i “beyond” ED, we must admit that the indications “passed” into the real word and approved are very few, as we can count them with one hand. This is an inherent limitation of the underlying model targeting PDE5 and/or of the molecule

or is the result of the planetary success of PDE5i for ED that steals space to any other possible use? Thus it was nontrivial to quantify any “other” use of PDE5i. By considering the number of papers published in various indications as a form of interest and/or consensus, before and after any official approval, our results suggests that the main secondary field of application is, currently, the cardiovascular one (43%) and this is supported by the fact that the PDE5i were thought to target vessels. Unfortunately the treatment of PAH, that alone accounts more than 28% of the total, is the only secondary indication now approved. The reported studies dealing with other uses (n:815; 22% of total) are actually off-label, therefore we are not allowed to hypothesize a role of PDE5i except some emerging evidences on possible applications in benign prostate syndrome, HF with preserved ejection fraction, Alzheimer and cognitive diseases.

Thus the potential of PDE5i can be considered exhausted? It is reasonable to expect more by enlarging the perspective towards other PDEs? Indeed the PDE super family is ubiquitously distributed in eukaryotes, thus it still represents a good opportunity to develop new therapeutic approaches, especially in emerging diseases. One of the possibilities is certainly to target, with a molecular approach, specific PDE subtypes, in physiological and pathological states, to revamp the therapeutic approach to intracellular signaling.

In conclusion, the lesson we have learned from the paradigmatic case of Sildenafil is that the development and the marketing of drugs is a complex multi factorial phenomenon that includes: 1- the potential and effectiveness of the molecules, 2- the beliefs and, often, the curiosity of the researchers, 3- the relationship between doctor and patient in terms of expectations and, last but first of all, 4- the economical interest related to their economic exploitation and the patent protection strategies. In each of the above steps, we can say, without doubt, that serendipity, still, can help [39]. Finally, a question that deserves

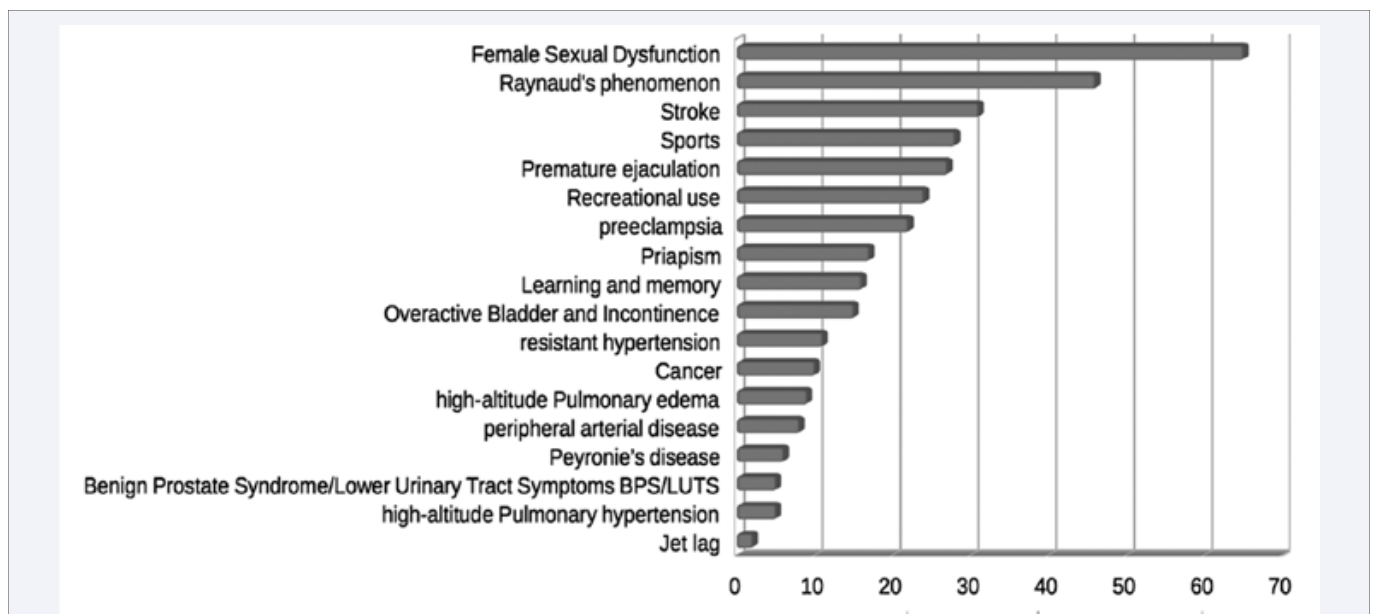


Figure 3 A line bar graph showing minor uses of PDE5i reported in the papers retrieved from MedLine. The scale reports the absolute number of papers for each indications.

a further elucidation is whether an extensive and, indeed, very profitable economic exploitation of a drug, focused to a specific use, steals space to any other possible uses making re-marketing a hard issue?

LIMITATIONS OF THE REVIEW

This study has several limitations that should be acknowledged. Firstly, the key words used are assumed as reference, only documents matching are thus included; secondly, a paper describing an off-label use does not necessarily support a possible future clinical use; thirdly, MedLine is continuously expanding, thus our data our data refer to April 2017.

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