COMMENTARY

Drugs acting on central nervous system (CNS) targets as leads for non-CNS targets [v1; ref status: indexed, http://f1000r.es/2wf]

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Abstract

Out-of-the-box approaches are currently needed to replenish the souring pipelines of pharmaceutical companies across the globe. Here a theme is presented – the use of central nervous system (CNS) drugs as leads for non-CNS targets. The approach is related to the use of existing drugs for new indications. Suitable chemical modifications of the CNS drugs abolish their CNS penetration. These novel analogs may then be screened for activity against non-CNS targets. Careful selection of the appropriate structural modifications remains the key to success.

Article Status Summary

Referee Responses

Referees	1	2	3
v1 published 06 Feb 2014	report	report	report

1 **Vijay Gokhale**, University of Arizona USA

2 **Evans Coutinho**, Bombay College of Pharmacy India

3 **Hariprasad Vankayalapati**, University of Utah USA

Latest Comments

No Comments Yet

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Commentary

The pharmaceutical industry worldwide is suffering from 'productivity crisis'[1]. The number of new molecular entities (NMEs) launched annually has decreased significantly despite rising discovery and developmental expenses[2]. Drug discovery researchers have started seeking approaches with higher probabilities of success. Drug repositioning, drug rescue and related strategies such as selective optimization of side activities (SOSA) are the front-runners[3]. In May 2012, the US National Institutes of Health (NIH) launched 'Discovering New Therapeutic Uses for Existing Molecules', a collaborative program administered by the National Center for Advancing Translational Sciences (NCATS). Such an initiative emphasized the importance of lead discovery approaches based on existing drugs.

The design and development of drugs that cross the blood-brain barrier (BBB) and act at some target site(s) in the central nervous system (CNS) is a formidable task. In contrast, for the drugs to act on peripheral targets, it is important to restrict their passage through the BBB in order to avoid unwanted CNS side effects. Several physicochemical and molecular properties of CNS drugs differ from peripherally acting drugs; the former have lower molecular weights, are more lipophilic, have a smaller polar surface area (PSA), a fewer H-bond acceptors and donors and fewer rotatable bond[4]. There is a fine balance between the physicochemical properties of CNS and non-CNS drugs.

During typical lead optimization cycles in the discovery phase, the lead molecules undergo several chemical modifications in order to improve their potency and pharmacokinetic properties, which usually lead to increased a) molecular weight, b) lipophilicity, c) molecular complexity, d) number of rotatable bonds, e) number of H-bond donors and acceptors, etc[5]. In general, the drugs are more complex than the leads and exhibit higher values for the majority of the associated molecular properties listed above. Based on these findings, it can be hypothesized that 'CNS drugs which are smaller and lower ranges of the aforementioned molecular properties make excellent starting points (as leads) for the development of non-CNS drugs'. Several aspects of this hypothesis are outlined in the discussion given below.

The majority of the CNS drugs are basic in nature. The presence of an ionizable functional group (mostly cationic) favors BBB penetration. Strong acids ($pK_a < 4$) and strong bases ($pK_a > 10$) are prohibited from crossing the BBB[4]. Chemical modifications of the basic functional group (primary and secondary) to a neutral species (e.g., conversion of primary amine to a substituted urea or amide) may impede the entry of the NME into the CNS. Several physicochemical and molecular properties can then be tailor-made once suitable potency against a non-CNS target is found.

Another molecular property, PSA, is crucial for BBB penetration. A PSA cutoff of 90 $Å^2$ has been suggested for CNS drugs[6]. Increased PSA is likely to create hurdles in the passage of NMEs across the BBB. An increased PSA can be achieved through the introduction of polar functional groups such as sulfonamide, carboxylic acid, substituted amides, etc., on the aromatic rings present in majority of the CNS drugs. Structural modifications leading to a higher PSA will ultimately lead to an increased number of H-bond donors and acceptors and reduced lipophilicity. The cumulative effect is reduced CNS penetration.

CNS drugs tend to have less molecular flexibility, lighter molecular weights and less molecular volume[4]. Significant increases in these molecular properties may create obstacles in absorption following oral administration leading to reduced bioavailability, e.g., an increased number of rotatable bonds can result in increased hepatic metabolism of the drug[7]. Nonetheless, the overall effects of an increase in the molecular weight and/or molecular flexibility on BBB penetration may depend on alterations in other properties such as lipophilicity and PSA.

In terms of toxicity, inhibition of the hERG channel by several CNS drugs (e.g., haloperidol) is a major concern. Many CNS drugs contain the hERG pharmacophore (aromatic rings and suitably placed cationic N)[8]. Suitable chemical modifications of the CNS drugs such as attenuating the basicity of the cationic N and suitably placed aromatic substituents may lead to abolished hERG binding and associated adverse effects. Thus, conversion of a CNS drug into its non-CNS counterpart, according to the theme of this commentary, may lead to diminished hERG toxicity.

From the above discussion, it appears convincing that the CNS drugs can serve as suitable leads for non-CNS targets after appropriate structural modifications leading to considerable alterations in their property space. This leads to the question: what are the potential applications of such a strategy?

Combinatorial libraries starting with CNS drugs can be designed *in silico* and then synthesized after selecting desirable substituents to introduce structural novelty (see Figure 1). These libraries may be unique in terms of structural and property space due to their origin from a known drug and thus may serve as a novel compound collection for high-throughput screening (HTS) campaigns. Once suitable hits are identified, development time may be reduced because of prior knowledge of the original drug. The pharmacokinetics (PK), pharmacodynamics (PD), adverse reactions, toxicity and the clinical trials data obtained from the original drug may guide the design of such experiments for the non-CNS analogs. Similarly, the synthetic routes, bulk scale-up and the analytical methods may also be used for the novel non-CNS derivatives. The utility of any and every piece of information about the CNS drug may vary from case to case. Since the original drug was never intended for a peripheral target, the intellectual property issues (novelty, non-obviousness) between the peripheral analogs and the original drug analogs for the CNS target may be minimal.

Some functional groups convey particular therapeutic effects, e.g., acetic acid or related aliphatic acids as analgesic and anti-inflammatory agents (diclofenac, ibuprofen), sulfonamides as carbonic anhydrase (CA) inhibitors and as anti-bacterials (sulfisoxazole). As such introduction of such functional groups during chemical modifications of CNS drugs may lead to a gain in potency for non-CNS targets such as CA. Careful selection of the chemical modifications aimed at the non-CNS target coupled to virtual screening of the designed analogs may potentially increase the rate of success of this approach.

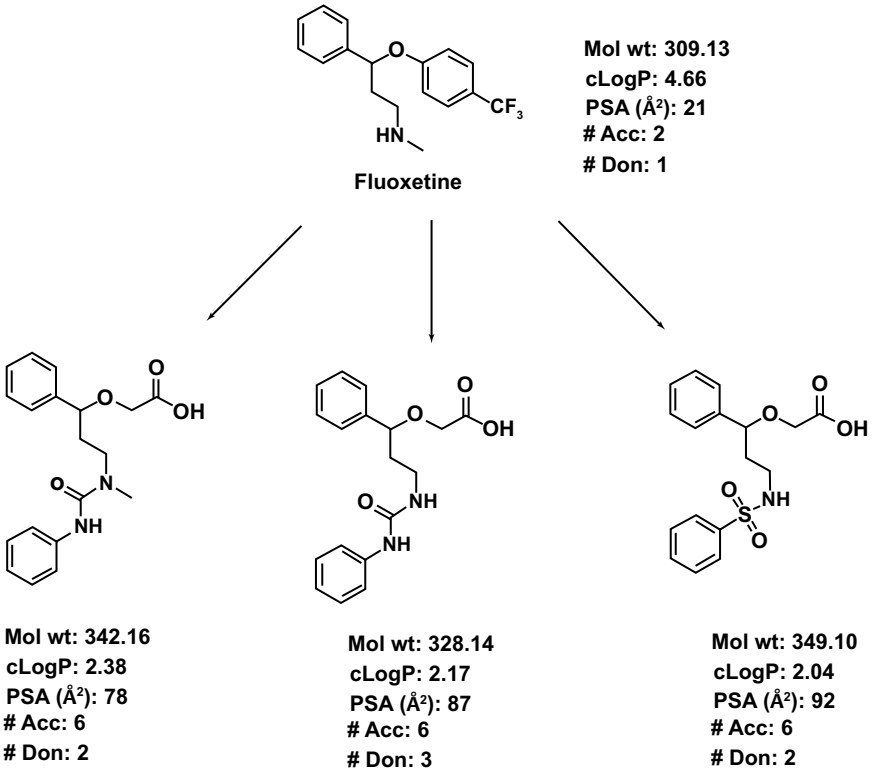

Figure 1. An illustration of the concept of using CNS drugs for non-CNS targets. Fluoxetine, an antidepressant agent, is used as a template. The synthesis of the analogs can be achieved by modifying the synthetic route of fluoxetine itself. The major structural modification includes abolishing the basicity of the secondary N in fluoxetine by converting it to urea or sulfonamide. Similarly, the 4-CF_3Ph ring is replaced with an acetic acid side chain. The resultant structural modifications lead to increased PSA, decreased cLogP (calculated logarithm of partition coefficient) and an increased number of H-bond donors and acceptors.

In summary, the commentary outlines a novel approach for generating 'interesting' compound collections for lead discovery. Such an idea is of potential interest in times of pharmaceutical 'productivity crisis'. The designed libraries can be tailor-made to suit the target requirements for potency and/or selectivity, in addition to pharmacokinetic and toxicity properties. Compared to the traditional lead discovery method based on HTS (with or without virtual screening) of in-house or commercially available compound collections, the 'intelligent' (virtual or physical) libraries developed using established CNS drugs may yield higher success rate (% of hits).

Conclusion

The use of CNS drugs as a starting point for developing non-CNS leads seems interesting with reference to potentially altered molecular, pharmacokinetic, pharmacodynamic and/or toxicity properties. The combinatorial libraries based on the CNS drug scaffolds may perturb novel chemical space not accessed previously by the non-CNS small molecule drugs. Curious researchers interested in the above strategy may help in demonstrating its potential utility.

Competing interests

No competing interests were disclosed.

Grant information

The author(s) declared that no grants were involved in supporting this work.

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References

1. Paul SM, Mytelka DS, Dunwiddie CT, *et al.*: **How to improve R&D productivity: the pharmaceutical industry's grand challenge.** *Nat Rev Drug Discov.* 2010; **9**(3): 203–214.
PubMed Abstract | Publisher Full Text
2. Mullard A: **2011 FDA drug approvals.** *Nat Rev Drug Discov.* 2012; **11**(2): 91–94.
PubMed Abstract | Publisher Full Text
3. Mullard A: **Could pharma open its drug freezers?** *Nat Rev Drug Discov.* 2011; **10**(6): 399–400.
PubMed Abstract | Publisher Full Text
4. Pajouhesh H, Lenz GR: **Medicinal chemical properties of successful central nervous system drugs.** *NeuroRx.* 2005; **2**(4): 541–553.
PubMed Abstract | Publisher Full Text | Free Full Text

5. Oprea TI, Davis AM, Teague SJ, *et al.*: **Is there a difference between leads and drugs? A historical perspective.** *J Chem Inf Comput Sci.* 2001; **41**(5): 1308–1315.
PubMed Abstract | Publisher Full Text

6. Hitchcock SA, Pennington LD: **Structure-brain exposure relationships.** *J Med Chem.* 2006; **49**(26): 7559–7583.
PubMed Abstract | Publisher Full Text

7. Veber DF, Johnson SR, Cheng HY, *et al.*: **Molecular properties that influence the oral bioavailability of drug candidates.** *J Med Chem.* 2002; **45**(12): 2615–2623.
PubMed Abstract | Publisher Full Text

8. Perry M, Stansfeld PJ, Leaney J, *et al.*: **Drug binding interactions in the inner cavity of hERG channels: molecular insights from structure-activity relationships of clofilium and ibutilide analogs.** *Mol Pharmacol.* 2006; **69**(2): 509–519.
PubMed Abstract | Publisher Full Text

Current Referee Status:

Referee Responses for Version 1

Hariprasad Vankayalapati
Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA

Approved with reservations: 07 March 2014

Referee Report: 07 March 2014
This F1000Research article on "*Drugs acting on central nervous system (CNS) targets as leads for non-CNS targets*" submitted by Kharkar is on a subject not uncommon to the CNS research community.

The following comments need to be addressed:

1. The author should state that several CNS agents, particularly multifunctional targets, are currently in clinical trial or have been approved for the treatment of non-CNS diseases despite the fact that they can cause inflammation and cancer. However, recently reported targeted CNS agents can bring an opportunity for repurposing some of the non-CNS targets as well. (Reference: http://www.ncats.nih.gov/research/reengineering/rescue-repurpose/rescue-repurpose.html).

2. Abstract: "*Out-of-the-box approaches are currently needed to replenish the souring pipelines of pharmaceutical companies across the globe"* this statement is arguable and needs to be revised.

3. Page 2 paragraph 9: this may not be true and needs to be revised completely to something like - "*Even the slightest modification to the physicochemical and physiological properties of the entity proposed as the non-CNS target of interest may alter its medicinal chemistry and tractability. One therefore needs to conduct every phase of non-clinical/IND work and may not reduce the development time due to the different PK and PD profile of the newly designed entity. However this is true only for repositioned drugs for new indications*".

4. Figure 1: The introduction of just a -COOH functional group as a strategy may not abolish the CNS activity completely (-COOH is negatively charged at the physiological pH). There is no evidence to support Figure 1 because reports show that at least 3–4% of CNS drugs have a carboxylic acid group. The author should therefore emphasize that this proposal is just theoretical as yet.

The author also missed some important references that I feel need to be included to support this article:

a) Gosh *et al*., (2012) Knowledge-Based, Central Nervous System (CNS) Lead Selection and Lead Optimization for CNS Drug Discovery. *ACS Chem. Neurosci.* 2012, 3, 50–68

b) Palmer and Alavijeh (2012) Translational CNS medicines research. in *Drug Discov Today*.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Competing Interests: No competing interests were disclosed.

Evans Coutinho
Bombay College of Pharmacy, Santacruz, Mumbai, India

Approved: 26 February 2014

Referee Report: 26 February 2014
The author has proposed a method of using CNS drugs as leads and developing them into candidates for non-CNS target. The logic behind the approach is to tailor the attributes of a) molecular weight, b) lipophilicity, c) molecular complexity, d) number of rotatable bonds, e) number of H-bond donors and acceptors and f) polar surface area that are in consonance with values appropriate for non-CNS agents. He has illustrated his point with fluoxetine as an example.

This is an idea is worthwhile looking at, but the final test would be to see some real applications of the approach on some established CNS drugs and their activity on some non-CNS targets experimentally established.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.

Vijay Gokhale
College of Pharmacy, University of Arizona, Tucson, AZ, USA

Approved with reservations: 10 February 2014

Referee Report: 10 February 2014
This commentary describes a general approach for using CNS-active drugs as leads for non-CNS targets. As physicochemical properties for CNS-active drugs are more restrictive than for non-CNS drugs, it would appear that the CNS-active drugs could serve as a good leads. It is a well-written commentary discussing general approaches to modify properties of these lead molecules. The approach is also exemplified by use of fluoxetine as a lead and some suggested modifications of it.

One main problem with this approach is the challenge of removing or minimizing CNS activity of these leads for non-CNS targets since the activity on CNS will lead to side effects. It would be useful to include a table comparing desired value ranges for different physicochemical properties (molecular weight, log D, polar surface area, hydrogen bond donor) for CNS and non-CNS drugs. I am not aware if this approach has been used in the medicinal chemistry literature. But if such reports exist, it would be good to include those references in the commentary.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Competing Interests: No competing interests were disclosed.