COMMENTARY

Drugs acting on central nervous system (CNS) targets as leads for non-CNS targets [v2; ref status: indexed, http://f1000r.es/35d]

Prashant S. Kharkar
Department of Pharmaceutical Chemistry, SPP School of Pharmacy and Technology Management, SVKM’s NMIMS, Mumbai, 400056, India

Abstract
Innovative drug discovery approaches are currently needed to rejuvenate the shrinking product pipelines of the 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.

Corresponding author: Prashant S. Kharkar (Prashant.Kharkar@nmims.edu)

How to cite this article: Kharkar PS (2014) Drugs acting on central nervous system (CNS) targets as leads for non-CNS targets [v2; ref status: indexed, http://f1000r.es/35d] F1000Research 2014, 3:40 (doi: 10.12688/f1000research.3-40.v2)

Copyright: © 2014 Kharkar PS. This is an open access article distributed under the terms of the Creative Commons Attribution Licence, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. Data associated with the article are available under the terms of the Creative Commons Zero "No rights reserved" data waiver (CC0 1.0 Public domain dedication).

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

Competing interests: No competing interests were disclosed.

First published: 06 Feb 2014, 3:40 (doi: 10.12688/f1000research.3-40.v1)
First indexed: 07 Mar 2014, 3:40 (doi: 10.12688/f1000research.3-40.v1)
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.

Majority of the CNS drugs are basic in nature\(^4\). The presence of an ionizable functional group (mostly cationic) favors BBB penetration. Strong acids (pK\(_a\) < 4) and strong bases (pK\(_\text{b}\) > 10) are prohibited from crossing the BBB\(^5\). 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, TPSA, is crucial for BBB penetration. A TPSA cutoff of 90 Å\(^2\) has been suggested for CNS drugs\(^6\). Higher

---

**Table 1. Comparison between CNS and non-CNS drugs in terms of associated properties**\(^7\).

| Molecular/Physicochemical property | CNS drugs | Non-CNS oral drugs |
|-----------------------------------|-----------|--------------------|
| No. of H-bond acceptors            | 0–5 (2–3) | 0–11 (3–4)        |
| No. of H-bond donors               | 0–3 (0–1) | 0–7 (2–3)         |
| Molecular volume (Å\(^3\))         | 800–1000 (740–970) | 1000–1200          |
| TPSA (Å\(^2\))                     | <76 (25–60) | >80 (80–140)      |
| No. of carboxylic acid groups\(^8\) | 0         | 0–2               |
| No. of basic amines                | 0–2       | 0–1              |
| No. of polar H atoms               | 0–3       | 0–6              |
| C-Het ratio (ratio of C atoms and non-C, non-H atoms) | 2.1–11 | 1.11–77.8 |
| Molecular weight                   | 100–450 (300–350) | 100–650 (350–400) |

---

\(^1\) Ghose et al. (2012)

\(^2\) The values in parentheses indicate the best ranges

\(^3\) Only 3–4% CNS drugs contain –COOH group whereas ~25% non-CNS oral drugs contain a –COOH group
TPSA is likely to create hurdles in the passage of NMEs across the BBB. This 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 TPSA will ultimately lead to an increased number of H-bond donors and/or acceptors and reduced lipophilicity. The cumulative effect is reduced CNS penetration.

The CNS drugs tend to have less molecular flexibility, lighter molecular weights and less molecular volume. 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. 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 molecular volume, solvent-accessible surface area (SASA), lipophilicity and TPSA. The distinction between the CNS and non-CNS oral drugs in terms of molecular and physicochemical properties is clearly evident from Table 1. Many of the common properties such as LogP, number of aromatic rings and ring assemblies and distribution coefficient [logD at pH 2 and pH 7.4] show little or no distinction between CNS and non-CNS oral drugs. Such properties were not included in Table 1.

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). 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, every phase of non-clinical/investigational new drug work will need to be carried out with the lead molecules as normal, which may not reduce the development time due to a

---

**Figure 1.** A theoretical 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$_3$Ph ring is replaced with an acetic acid side chain. The resultant structural modifications lead to increased PSA, decreased cLogP (calculated LogP) and an increased number of H-bond donors and acceptors.
potentially different PK/PD (pharmacodynamic) profile of the newly designed entity. The development time may be reduced if a CNS drug is repurposed for a non-CNS indication. Several CNS drugs have already been repurposed for non-CNS indications, e.g., thalidomide (sedative/hypnotic to multiple myeloma and leprosy), chlorpromazine (antihistaminic to anticancer - inhibitor of the mitotic kinesin KSP/Eg5)\(^1\), etc. Nonetheless, PK/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 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 non-CNS 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 these functional groups during chemical modifications of the 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.

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 based on HTS (with or without virtual screening) of in-house or commercially available compound collections, the ‘intelligent’ (virtual or physical) libraries developed using the 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, PK/PD 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.

**Acknowledgments**

The author acknowledges Dr. R. S. Gaud, Dean, SPP School of Pharmacy and Technology Management, SVKM’s NMIMS, Mumbai, India, for his help during preparation of this commentary.

**References**

1. Paul SM, Mytelka DS, Durwiniddie 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. Palmer AM, Alawieh MS: Translational CNS medicines research. Drug Discov Today 2012; 17(19–20): 1068–1076. PubMed Abstract | Publisher Full Text
5. Pajounest 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
6. 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(3): 1308–1315. PubMed Abstract | Publisher Full Text
7. Hitchcock SA, Pennington LD: Structure-brain exposure relationships. J Med Chem. 2006; 49(26): 7559–7583. PubMed Abstract | Publisher Full Text
8. 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
9. Ghose AK, Herbertz T, Hudkins RL, et al.: Knowledge-Based, Central Nervous System (CNS) Lead Selection and Lead Optimization for CNS Drug Discovery. ACS Chem Neurosci. 2012; 3(1): 50–68. PubMed Abstract | Publisher Full Text | Free Full Text
10. 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 ciclosporin and ibutilide analogs. Mol Pharmacol. 2006; 69(2): 509–519. PubMed Abstract | Publisher Full Text
11. Lee MS, Johansen L, Zhang Y, et al.: The novel combination of chlorpromazine and pentamidine exerts synergetic anti-proliferative effects through dual mitotic action, Cancer Res. 2007; 67(23): 11359–11367. PubMed Abstract | Publisher Full Text
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.
