INTRODUCTION
There is a lot of interest in identifying how drugs affect Central Nervous System, and possible strategies to counteract their effects. Pharmacotherapies acting over mechanisms mediating drug craving, withdrawal syndrome or relapse are being proposed.

OBJECTIVE
Identifying cell-surface receptors in the glutamatergic corticostriatal pathway between prefrontal cortex (PFC) and nucleus accumbens (NAc) proposed as therapeutic targets, as well as the pharmacotherapies targeting them, analyzing their efficacy on preventing relapse from cocaine-addiction, according to literature.

METHODS
Search in PMC with keywords “accumbens + prefrontal cortex + cocaine + addiction + glutamate + pharmacotherapy” was performed. 2 reviews were chosen among the results (Kalivas PW, 2011; Halle CN, see Portfolio for complete references).

Thereon, specific searches about each pharmacotherapy and target were made (for more information see Portfolio, Annex 3).

MECHANISM OF ACTION OF ADDICTIVE DRUGS

**DRUGS**

**Mesocorticolimbic dopaminergic pathway**

**Corticostriatal glutamatergic pathway**

**Nucleus accumbens**

**Mesocorticolimbic dopaminergic pathway**

**Corticostriatal glutamatergic pathway**

**Nucleus accumbens**

**Drugs**

**And other**

**Mesocorticolimbic dopaminergic pathway**

**Corticostriatal glutamatergic pathway**

**Nucleus accumbens**

**Trigging neuroadaptations that cause drug addiction**

**Figure 1.** Glutamatergic tripartite synapse between projections from PFC (yellow) with MSN (blue) and glia (green) in NAc. The surface receptors that have been pinpointed as targets for treating drug addiction are situated in their most common position, and identified in the key. In red, a dopaminergic terminal from the VTA.


**NMDA RECEPTORS (NMDAR)**

NMDAR are the mediators of LTP and LTD, by the regulation they exert over AMPAR expression on cell surface. NMDAR upregulation in MSN is also related to memory consolidation.

**AMPA RECEPTORS (AMPAR)**

Chronic Increased AMPAR levels in MSN, are highly related with cocaine addiction and relapse.

**DOPAMINE TRANSPORTERS**

Dopamine transporters are important modulators of glutamate transmission, acting like a “gate”.

**GLUTAMATE TRANSPORTERS**

Cocaine downregulates the presence and function of the cystine-glutamate exchanger (xCT) and GLT-1 in NAc. Their impairment causes a reduction of extrasynaptic levels of glutamate.

**MGLURII**

mGluR1 are autoreceptors. They regulate glutamate release. Cocaine intake reduces extrasynaptic glutamate, causing mGluR1 tone to decrease, thus increasing glutamate release from the presynaptic terminal. Chronic cocaine intake also downregulates mGluR1 expression.

**MGLURI**

mGluR5 and mGluR1 are postsynaptic receptors. Like mGluR1, they can regulate glutamate transmission.

**KEY for Figure 1 and Table 1:**

- Proteins regulating glial glutamate release and uptake, and therapies targeting them
- Metabotropic glutamate receptors (mGluRs), and therapies targeting them
- Ionotropic glutamate receptors (AMPAR, NMDAR), and therapies targeting them

**CONCLUSIONS**

Mechanisms elicited in NAc glutamatergic inputs from the corticostriatal pathway in addiction animal models offer potential targets for drug addiction therapy.

The projection from the PFC to NAc is an important site for addiction, but other neural pathways also modify NAc MSN homeostasis. This could explain some paradoxical results.

Pharmacological therapy can be a support for behavioral therapy, but will probably not become a substitute for it. Extinction learning is an active process and the cocaine-dependent subject must “learn” not to use the drug.

Usually, pharmacotherapies that inhibit one type of addiction are beneficial in other addictions, and even psychiatric disorders. The study of addiction might explain how are these processes related.

The study of these mechanisms may provide more insight into the processes implicated in different animal species: brain pathways, neuronal function and learning, reward and reinforcement mechanisms.