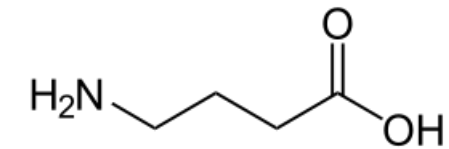
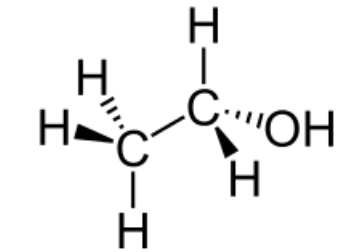
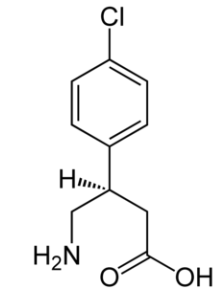
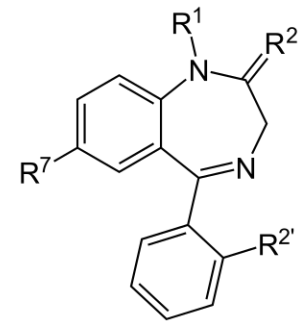
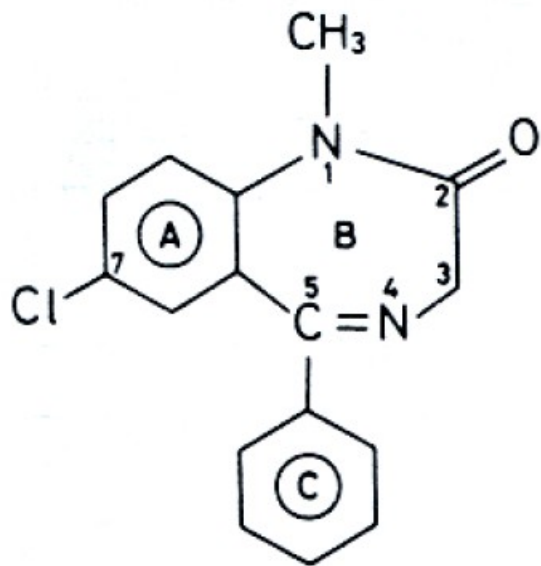


Dépendance aux bzd et Z-drugs



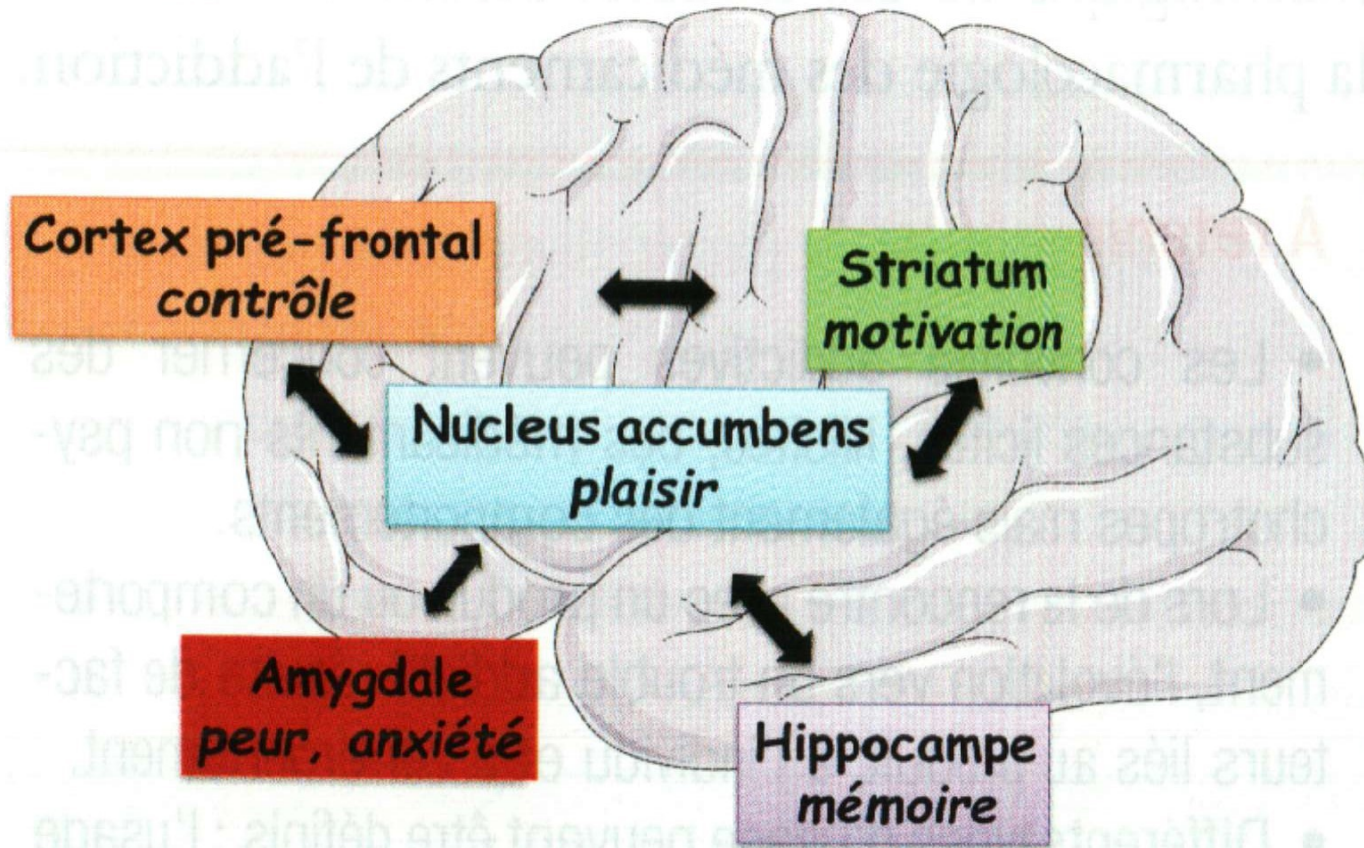
Dr D.Lamy

1,4 benzodiazépine

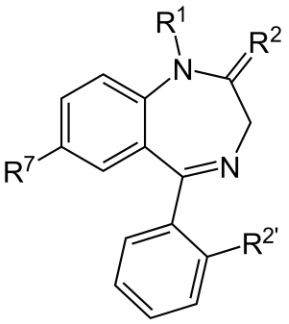


A = cycle benzène

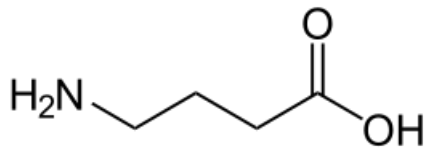
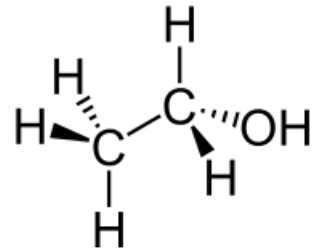
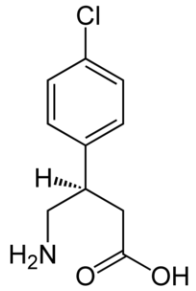
B = cycle 1,4 diazépine



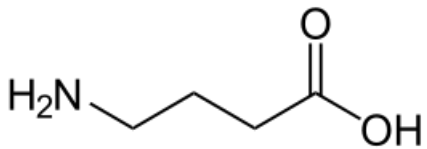
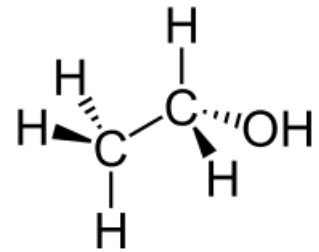
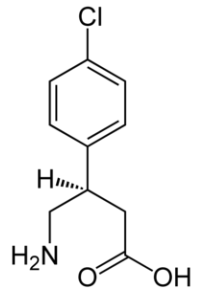
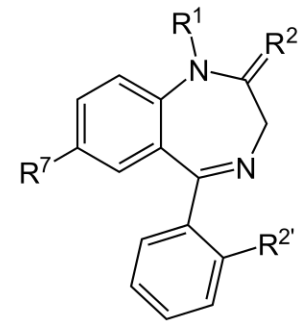
Dépendance aux bzd et Z-drugs



- Modèle cérébral de la dépendance
- Triangle bio-psycho-social
- Circuit de la récompense
- Récepteurs μ - dopamine
- Système GABA



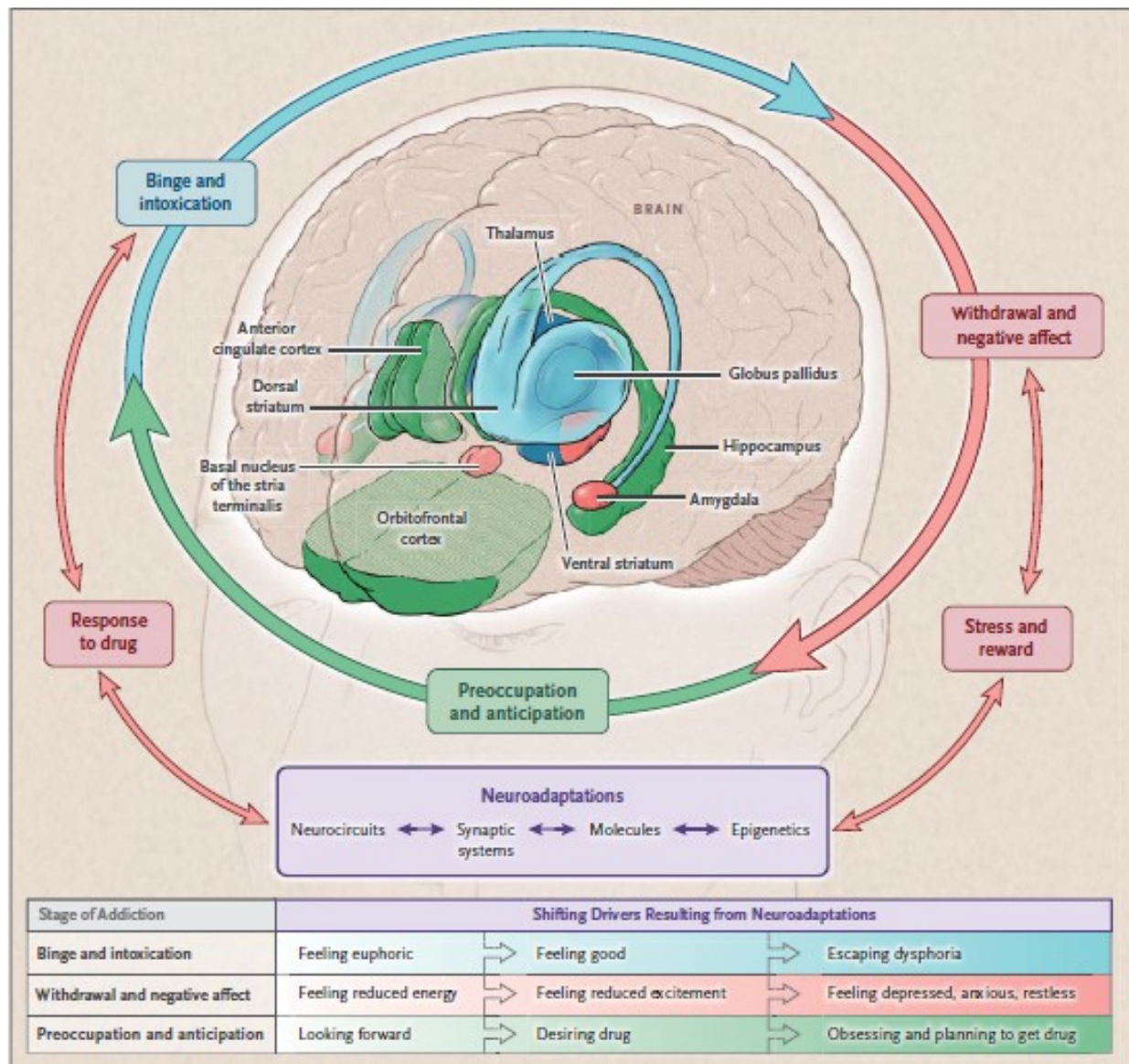
Modèle cérébral de la dépendance



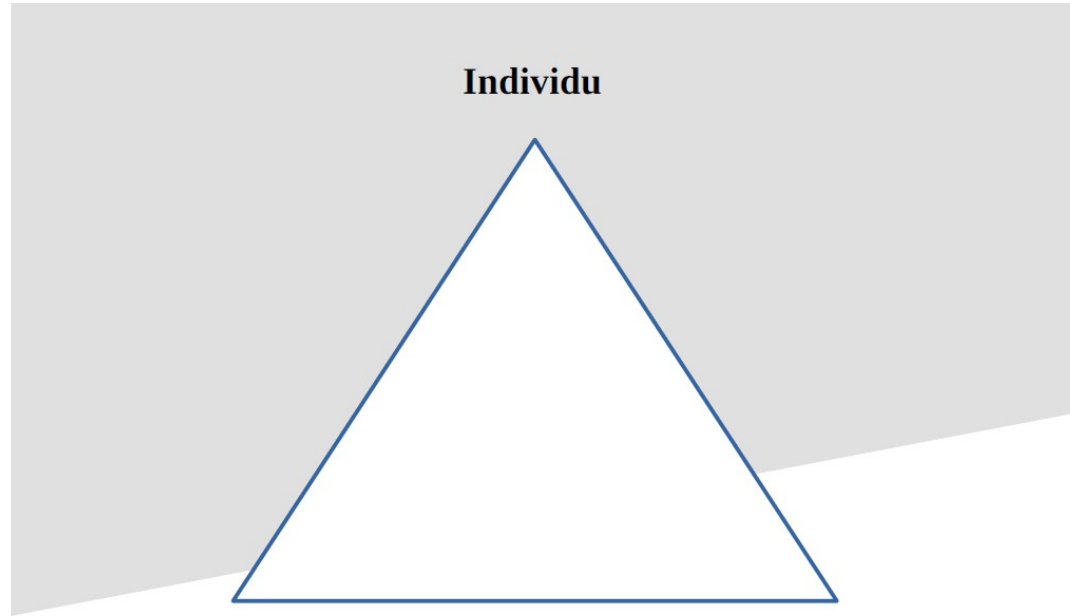
Neurobiologic Advances from the Brain
Disease Model of Addiction

Nora D. Volkow, George F. Koob, A. Thomas McLellan
New England Journal of Medicine 2016 ; 374:363-371

*National Institute on Drug Abuse (NIDA) at the
National Institutes of Health*



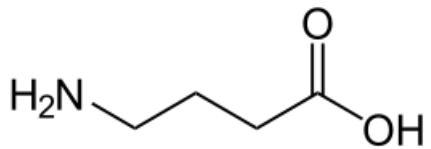
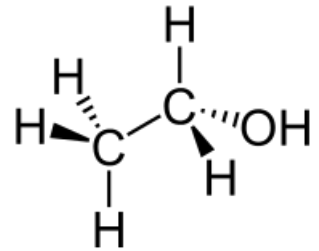
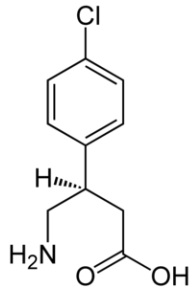
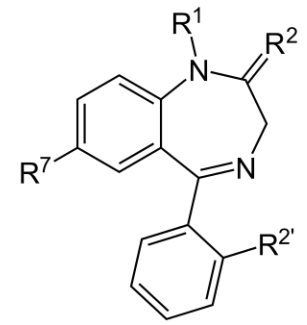
Triangle bio-psycho-social



Produit

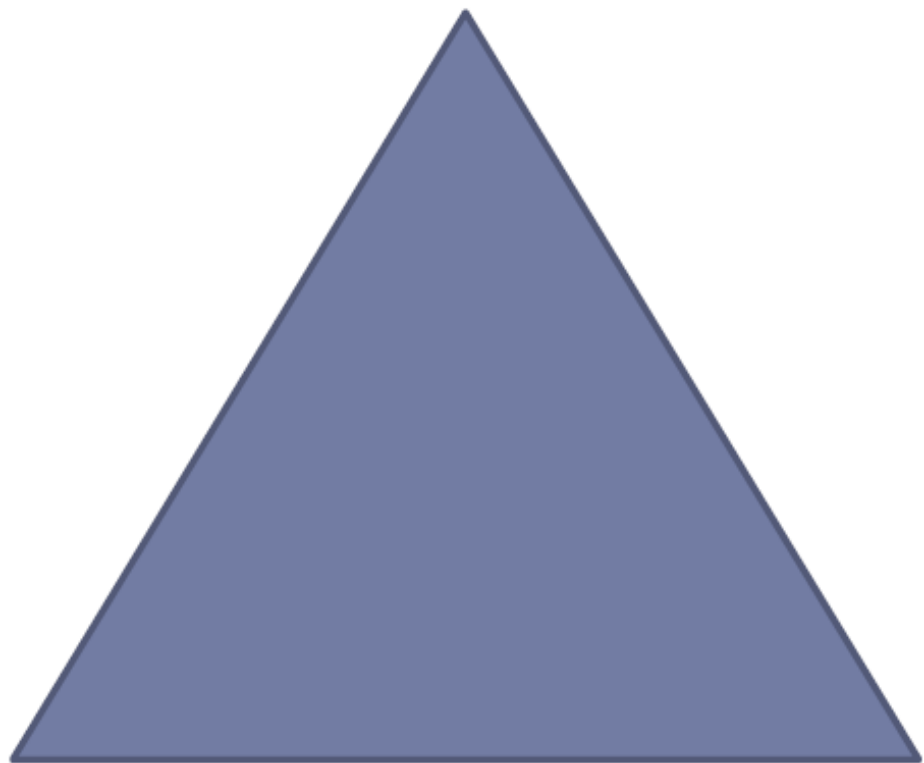
Environnement

Individu



Sensibilité individuelle

(facteurs génétiques, âge début de consommation, ...)



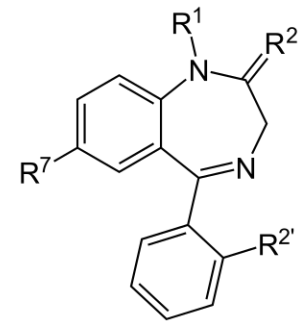
Type de produits

(tabac, héroïne, ...)

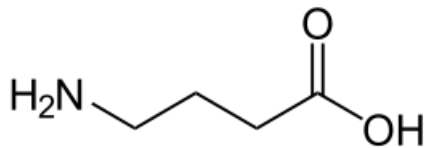
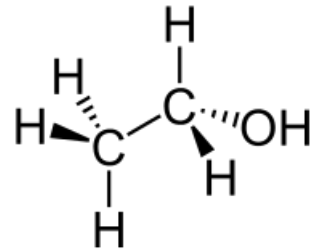
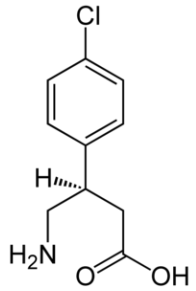
Environnement

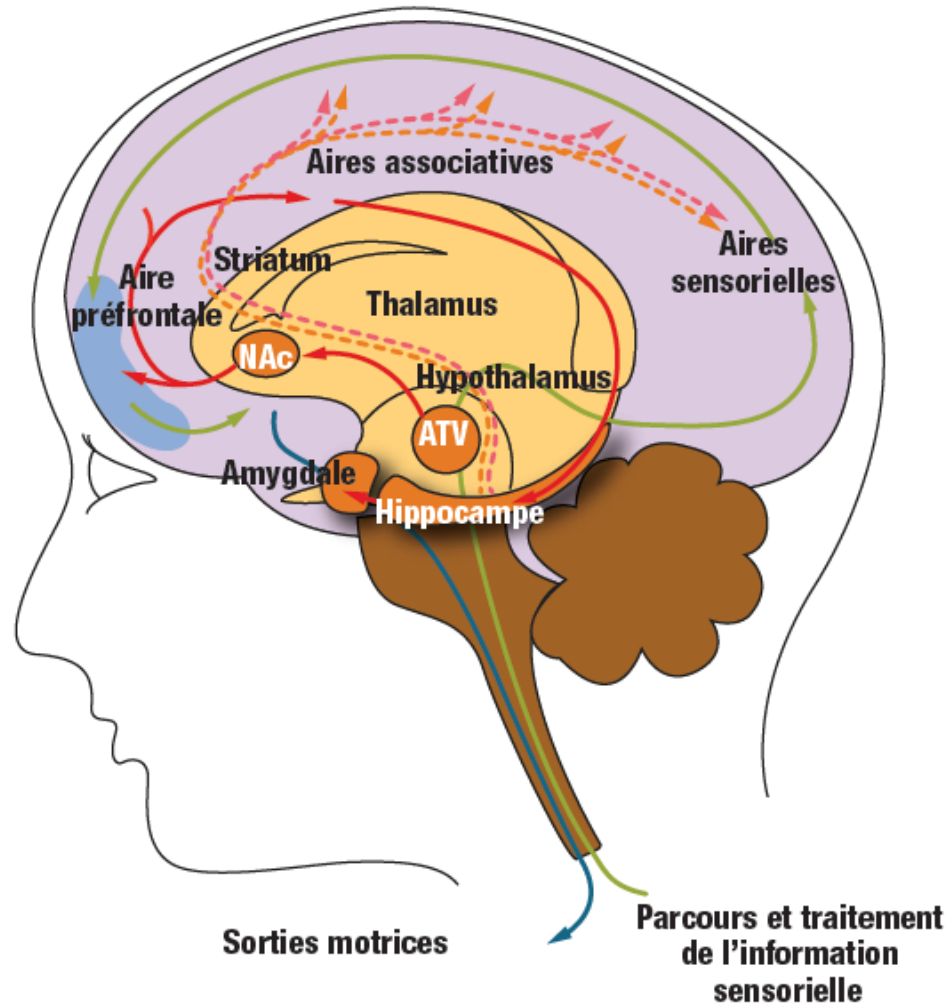
(**MG**, stress, entourage, ...)

Circuit de la récompense



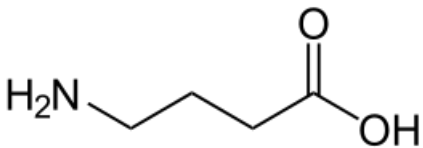
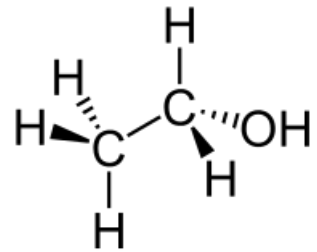
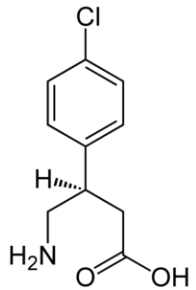
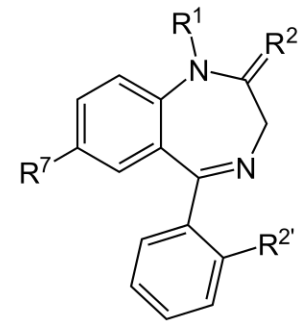
*Comportement amenant des effets positifs pour l'organisme ou satisfaisant le désir-besoin-projet déclenche un processus amenant plaisir, apaisement **et** enregistrement (associations contextuelles positives)*



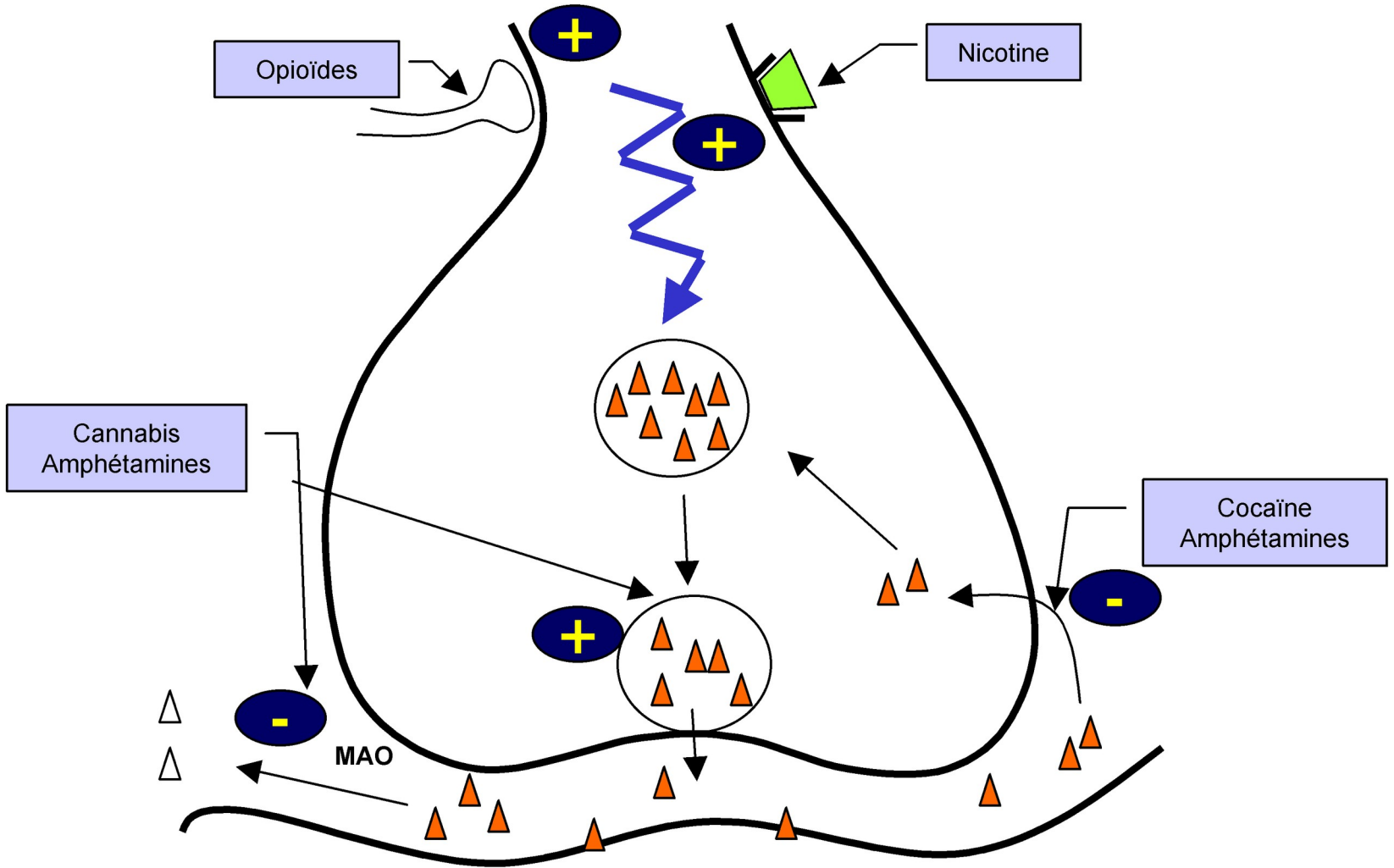


- NAc : noyau accumbens ;
- ATV : aire tegmentale ventrale ;
- : information sensorielle ;
- - : neurones sérotoninergiques ;
- - : neurones noradrénergiques ;
- - : neurones dopaminergiques ;
- - : sortie comportementale ;
- : cortex ; ■ : limbique ;
- : reptilien.

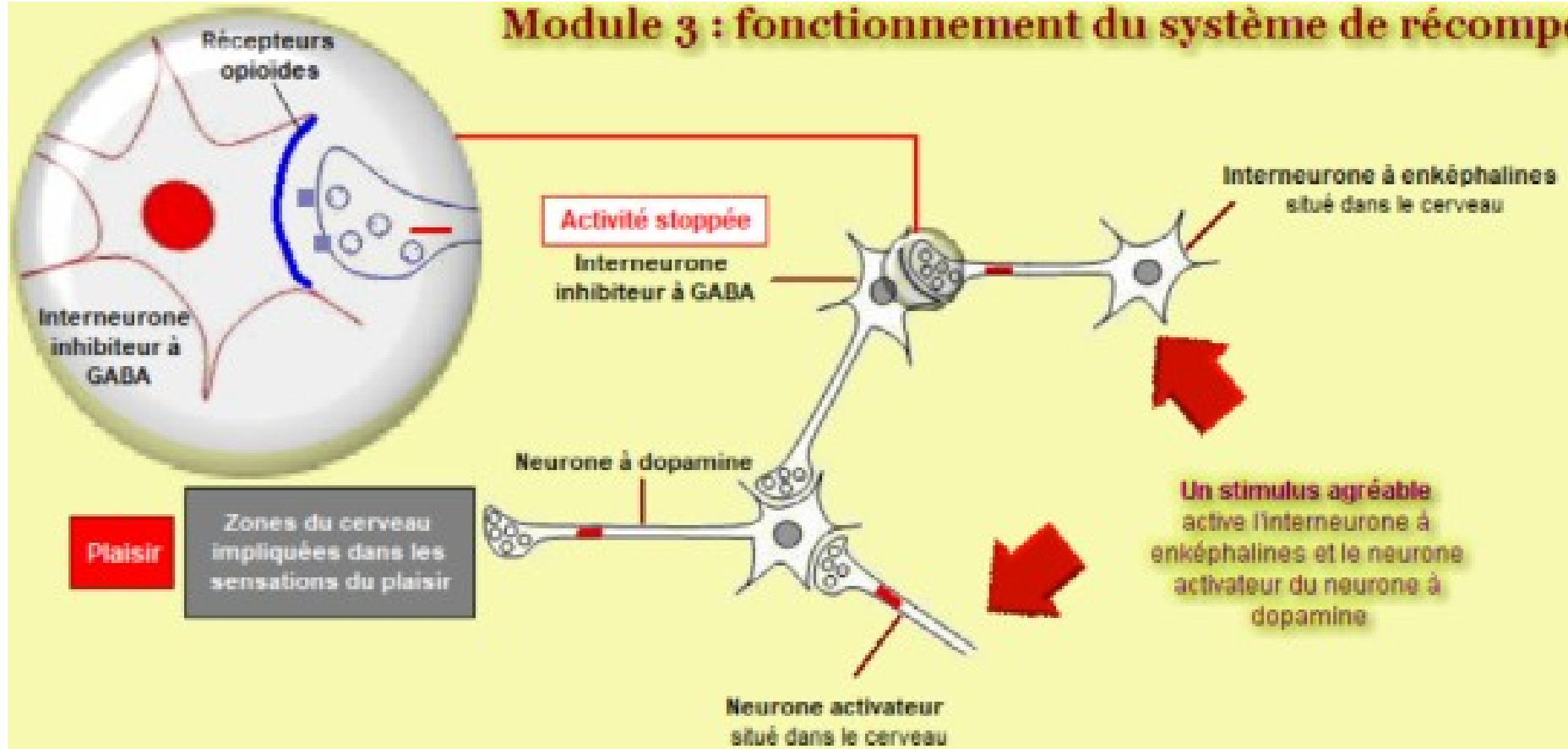
Récepteurs opiacés



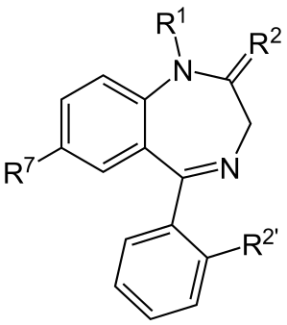
- Mu, Kappa, Delta
- Effets euphoriques médiés par les récepteurs Mu
- Les récepteurs Mu ont une affinité élevées pour les opiacés, les enképhalines et les beta-endorphines
- NB : la méthadone a une affinité principalement agoniste Mu (comme la morphine)



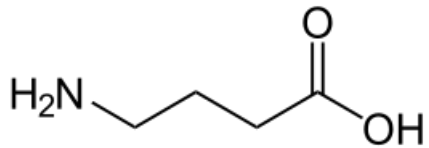
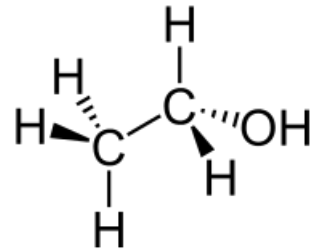
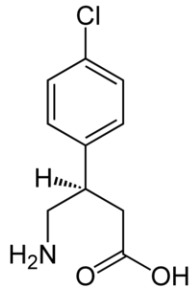
Module 3 : fonctionnement du système de récompense

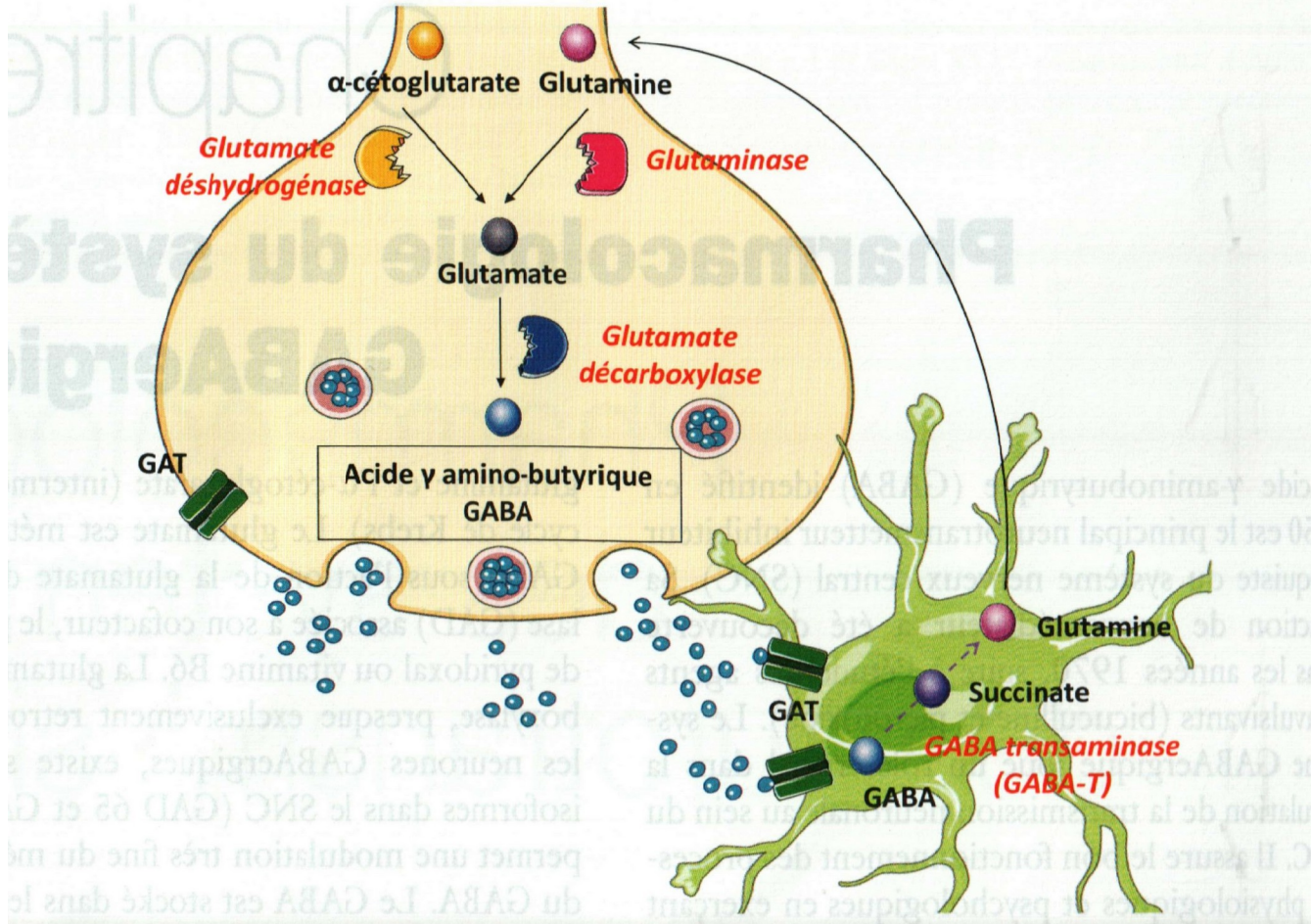


Le système GABAergique

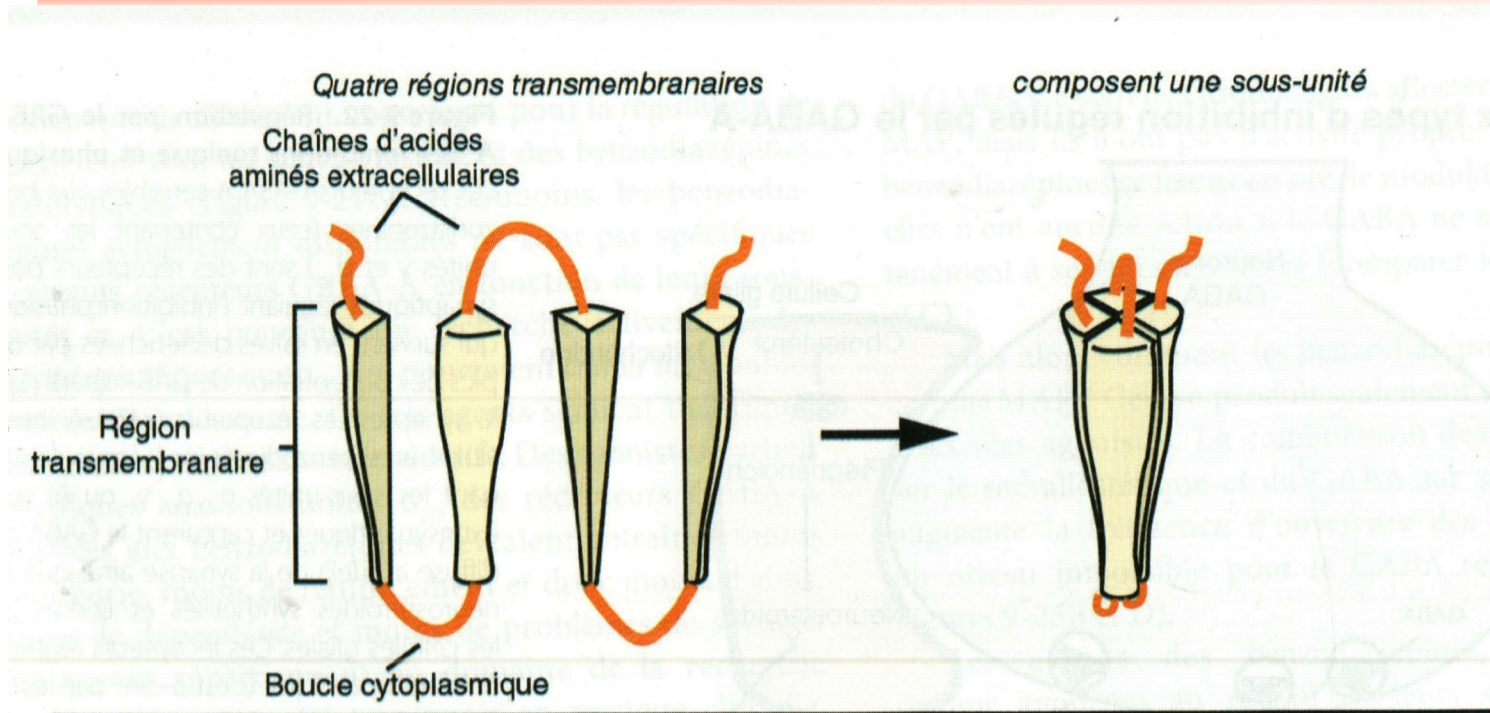
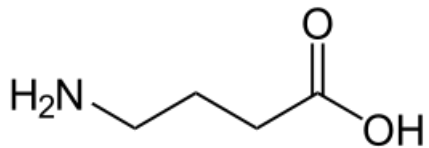
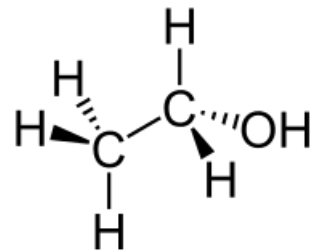
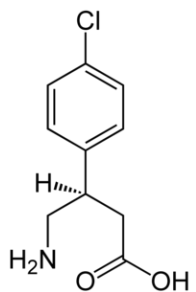
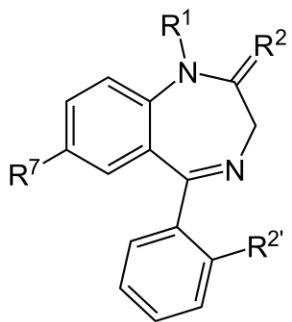


- Acide gamma-amino butyrique (1950)
- Neurotransmetteur inhibiteur ubiquiste du SNC
- Maintien de l'équilibre excitation/inhibition du cerveau
- Essentiellement des interneurones
- Rôle majeur des cellules gliales dans la synthèse



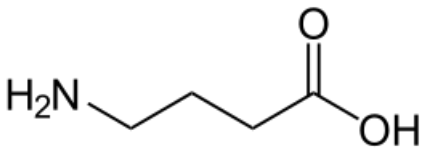
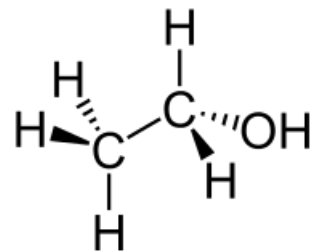
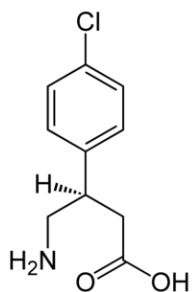
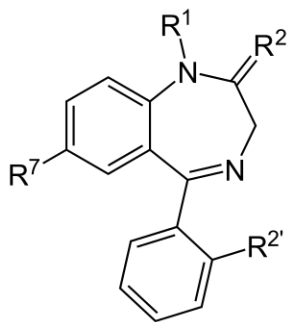


Structure des récepteurs GABA

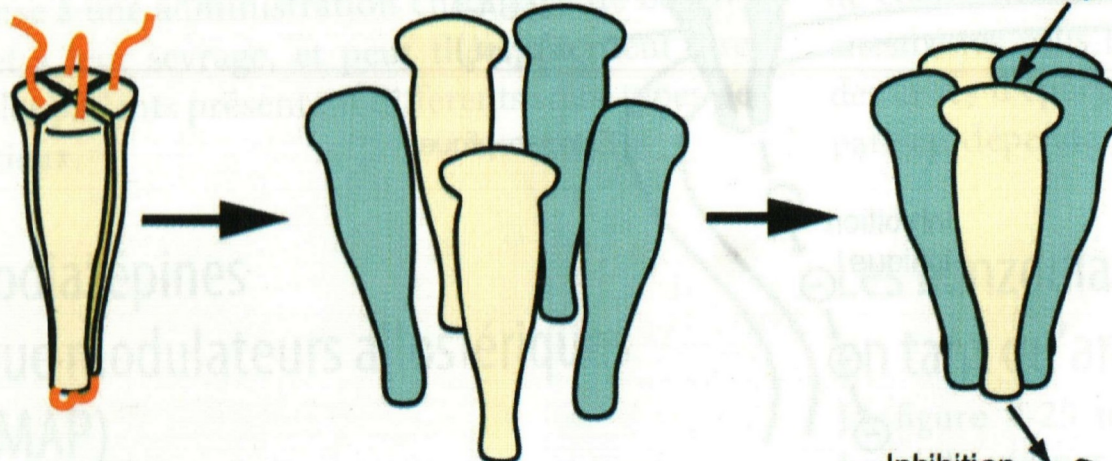


St.M.Stahl, in « Psychopharmacologie essentielle », 4ème édition

Structure des récepteurs GABA



Cinq structures forment le complexe récepteur

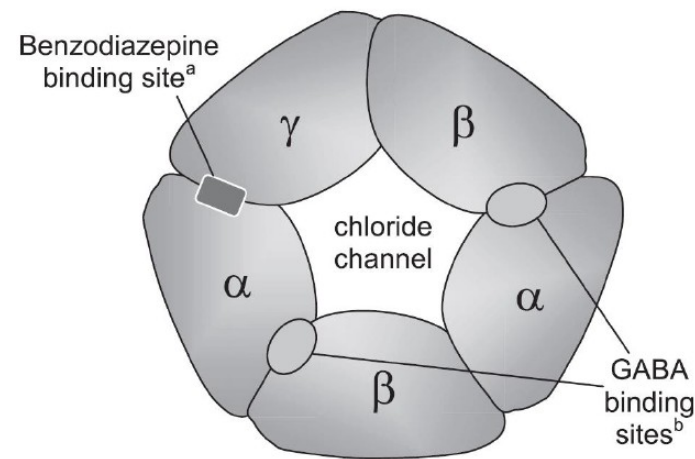
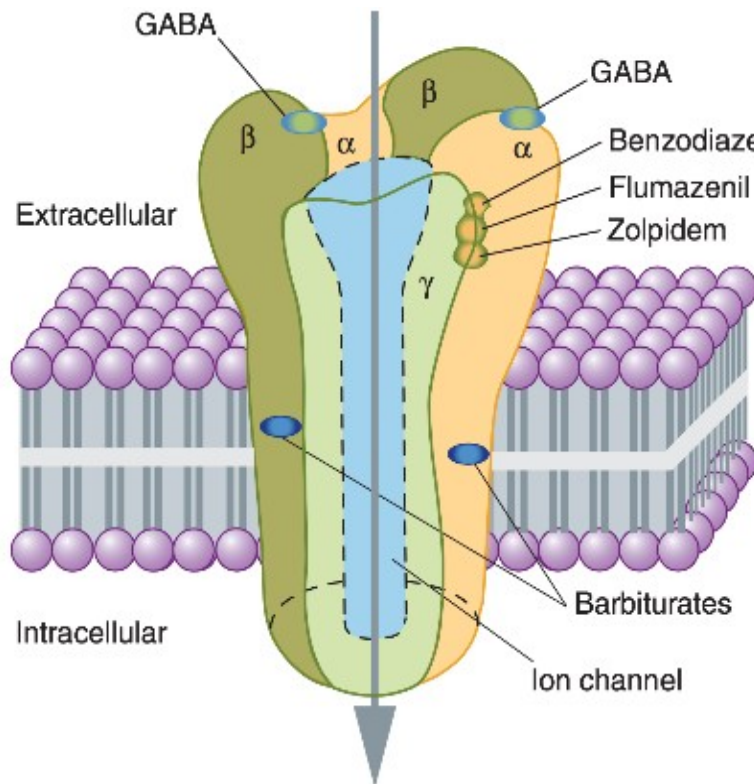
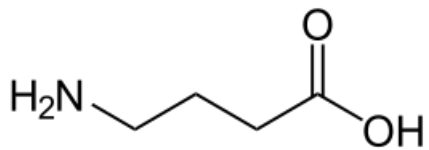
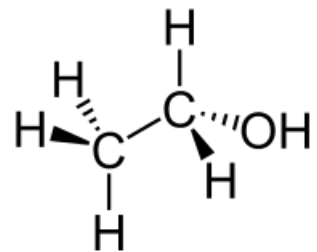
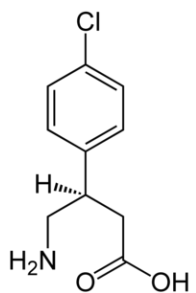
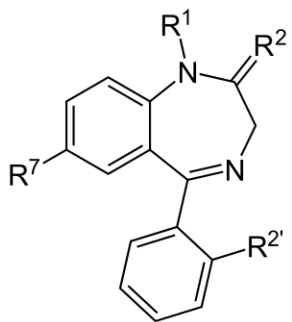


Le canal chlore est au centre

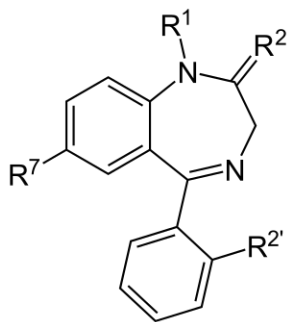
Inhibition ✓

St.M.Stahl, in « Psychopharmacologie essentielle », 4ème édition

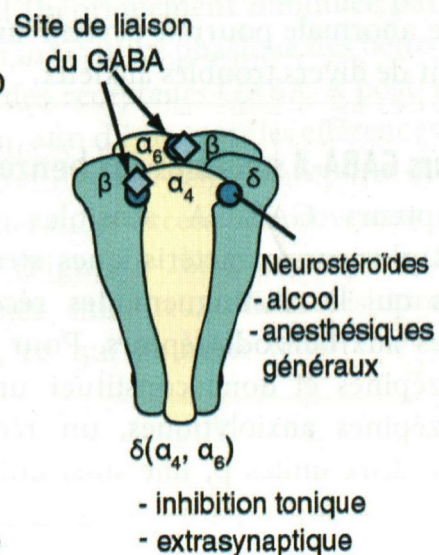
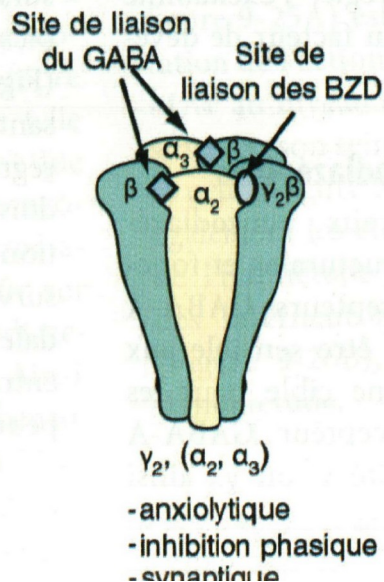
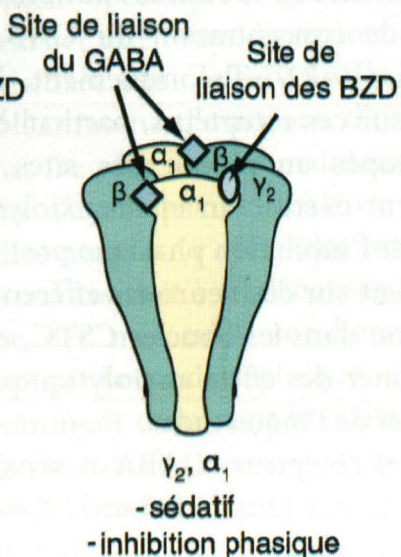
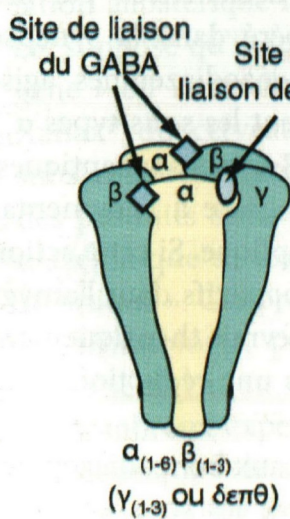
GABA et récepteurs



Structure des récepteurs GABA



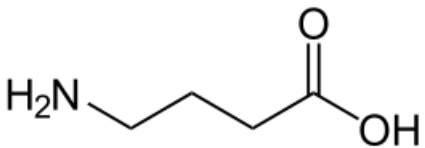
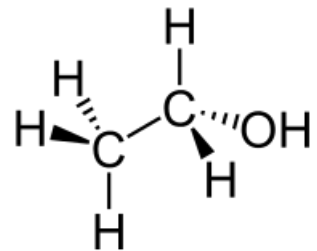
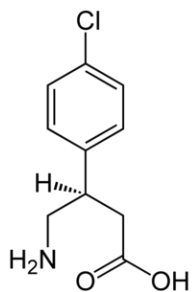
Sous-types majeurs de récepteurs GABA-A

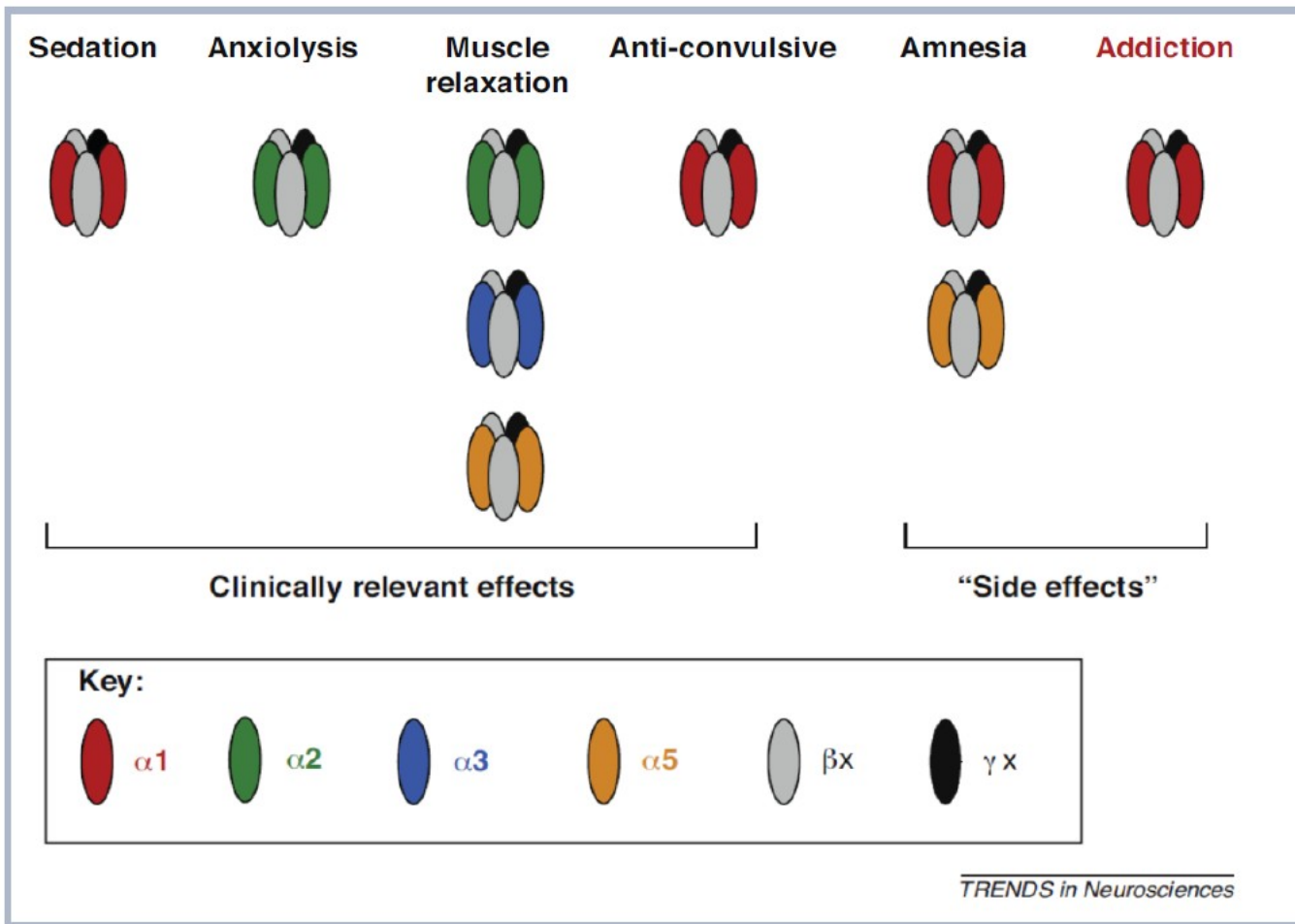


Neurostéroïdes
- alcool
- anesthésiques généraux

C

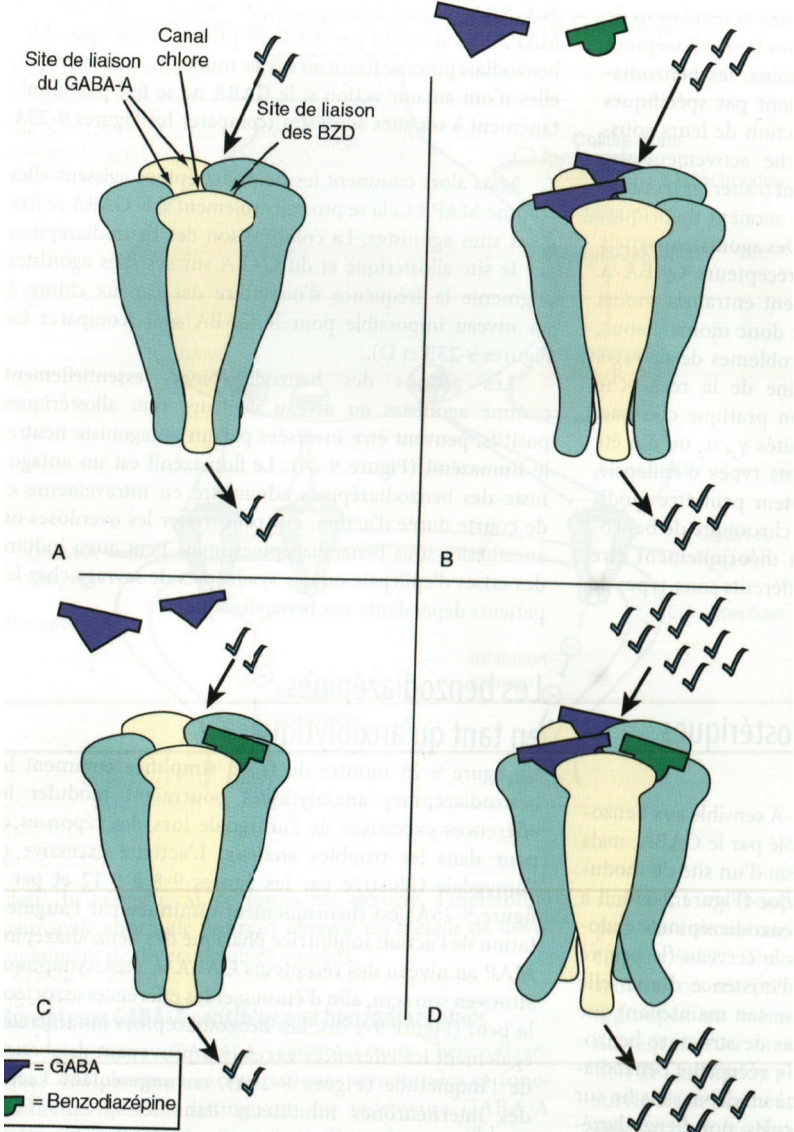
St.M.Stahl, in « Psychopharmacologie essentielle », 4ème édition





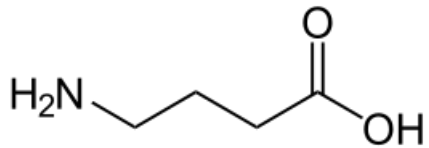
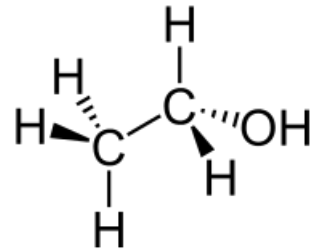
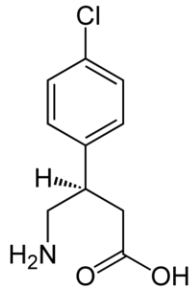
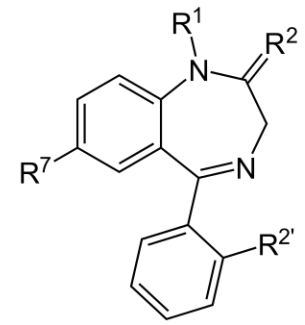
The past decade has seen an emerging understanding of the specific GABAAR subtypes responsible for mediating the diverse spectrum of BDZ pharmacological effects. For example, the sedative actions are known to be mediated by $\alpha 1$ -containing GABAARs, whereas the anxiolytic actions are mediated by $\alpha 2$ -containing GABAARs (TIPS 2011, Vol. 34, No. 4, p188)

Modulation allostérique



Histoire et prescriptions

- Opiacés (opium et ses dérivés)
- Barbituriques
- Antihistaminiques
- Hydrate de chloral
- Meprobamate
- Benzodiazépines (Librium 1958, Valium 1963)

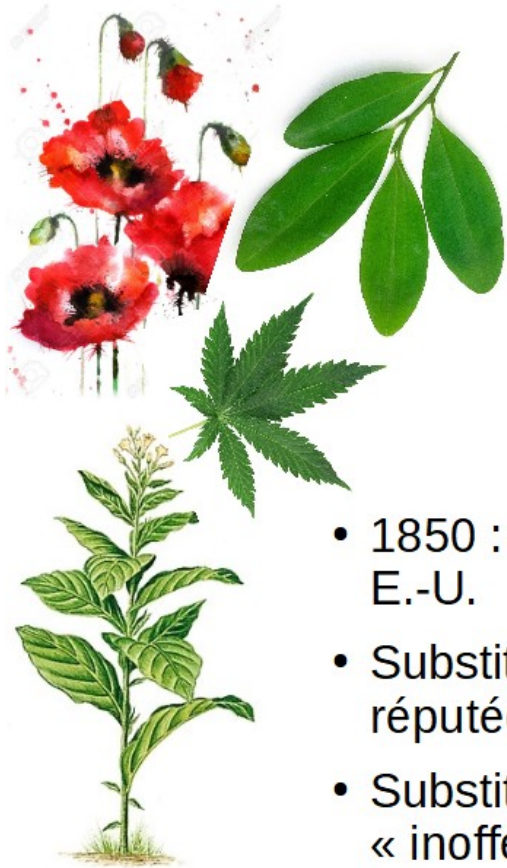




Le Lotus Bleu



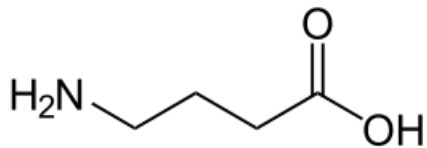
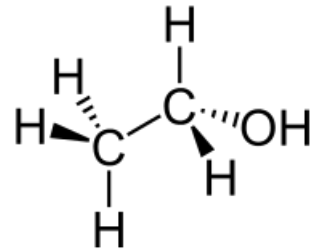
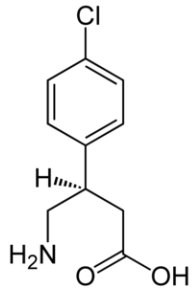
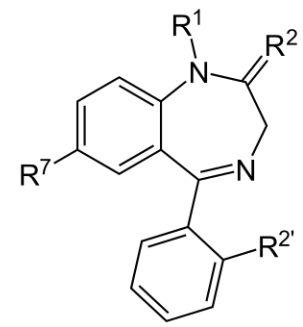
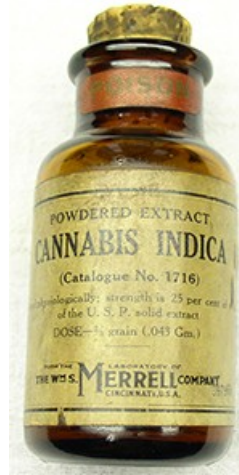
Opium



- 1850 : consommation d'opium largement répandue aux E.-U.
- Substitution par la morphine (découverte en 1804), réputée alors moins puissante et moins addictive
- Substitution par l'héroïne (découverte en 1874), substitut « inoffensif », préconisé en 1888 pour soigner la tuberculose
- Substitution par la méthadone (découverte en 1937 dans la recherche de nouveaux antidouleurs)

Facteurs de la dépendance

- Prescription médicale



Facteurs de la dépendance

Cocainum — Cocaïne.

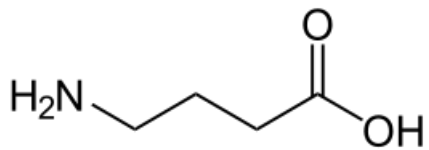
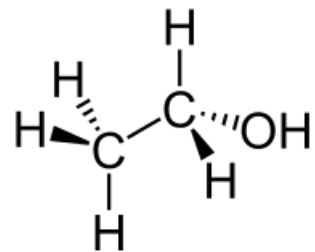
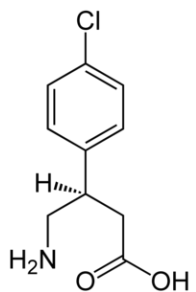
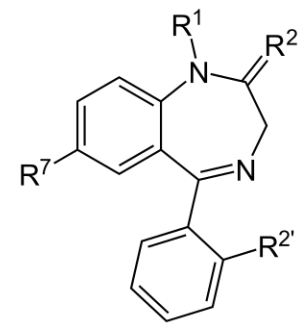
D. M. Chlorhydrate de cocaïne : 30 mg et 60 mg ; poudre de coca : 5 g et 10 g ; extrait fluide de coca : 5 g et 10 g ; teinture de coca : 25 g et 50 g.

R. Cocaini hydrochloridi
Benzophenoli
Mentholi
Usui externo.

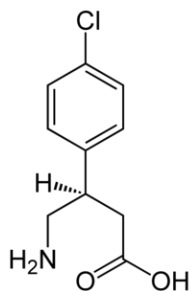
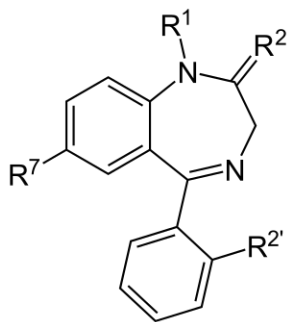
I g
I g
I g

Mélange de Bonain
Anesthésie du larynx,
du pharynx, du tympan.

59



Facteurs de la dépendance



Diamorphinum — Diamorphine — Héroïne N. D.

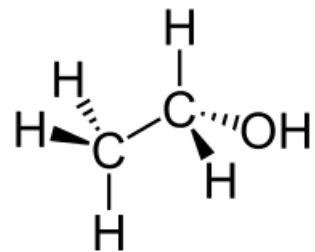
D. M. 5 mg et 15 mg.

R. Diamorphini Menthae aquae	25 mg 150 g	Toux rebelle
S. Une ou deux cuillerées à soupe à l'occasion des quintes violentes.		
R. Diamorphini Aqua	5 mg 1 g	Toux violente Grande douleur
fiat ampula n° I da tales n° tres.		

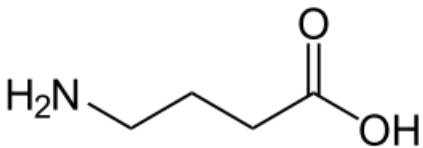
Aethomorphinum — Ethomorphine — Dionine N. D.

D. M. 50 mg et 150 mg.

R. Aethomorphini 10 mg

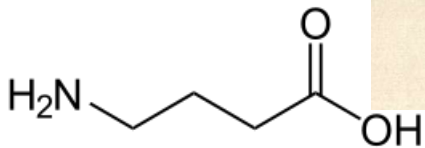
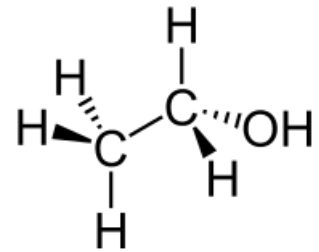
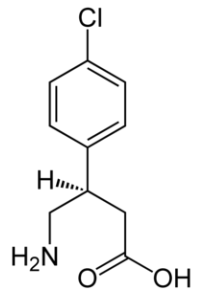
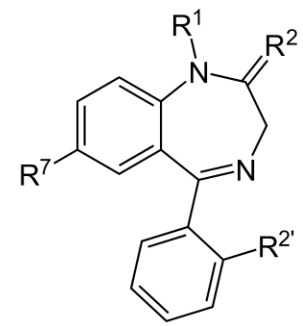


in La prescription médicale
par A.Simonart, 11ème édition, 1947



Therapie der **Morphiumsucht**

in Wilhelm Griesinger, Pathologie und Therapie der psychischen Krankheiten, 5ème édition, Berlin, 1892



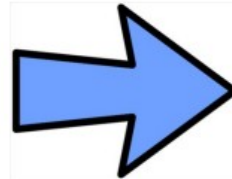
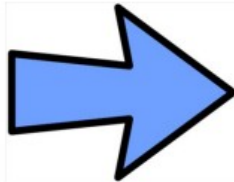
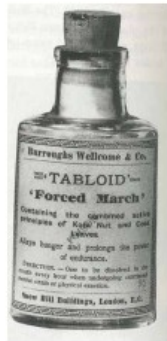
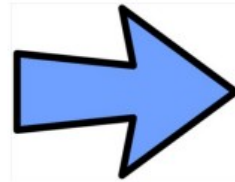
670

Drittes Buch. Erste Abtheilung. Dritter Theil.

ziehungsmethode ist die modificirte (E. Levinstein). Zuerst bestimmt man das tägliche Quantum, bei welchem der Patient sich erträglich fühlt. Im Allgemeinen ist der Grundsatz festzuhalten, dass man Morphium zu geben hat, wenn es nothwendig ist. Man kann die Kur wesentlich durch Cocaïn beschleunigen und unterstützen, aber nur mit absoluter Sachkenntniss; dem Zustande des Herzens muss immer Beachtung geschenkt werden. Gegen Schlaflosigkeit wirken die verschiedenen Hypnotica individuell. Doch kommen hauptsächlich Sulfonal, Amylenhydrat, Chloralamid und Chloral in Betracht.

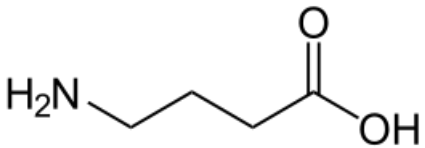
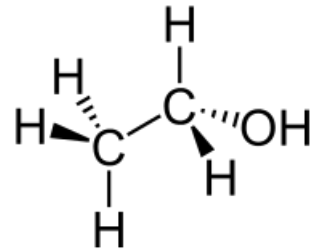
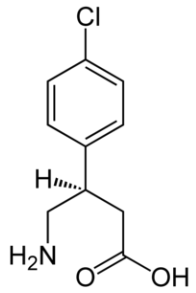
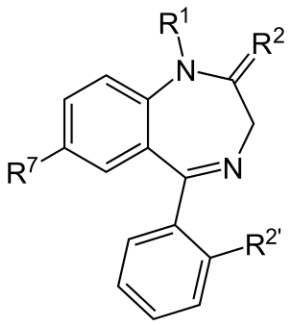
Mit der Entwöhnung von Morphium ist die Kur keineswegs beendet. Die Ursachen, um derenwillen der Kranke zum Morphinisten geworden, müssen beseitigt, die letzten Spuren der Intoxikation und Abstinenz getilgt, und die Persönlichkeit physisch widerstandsfähig gemacht werden.

Réponse du marché : production illicite

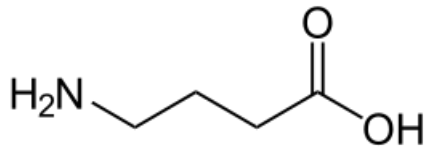
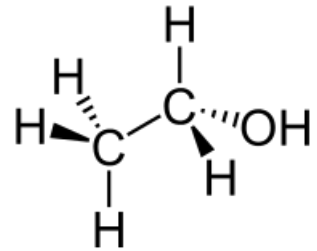
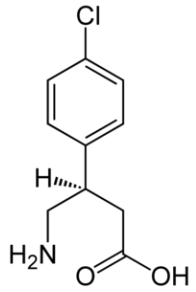
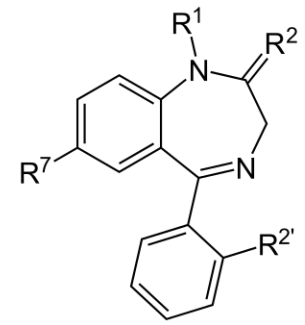


Dépendance aux bzd et Z-drugs

- Être humain = être de dépendance
- Mécanisme complexe et lié aux interactions de plusieurs cycles de neurotransmissions
- La rencontre du produit n'est pas anodine, il fut souvent prescrit
- Aujourd'hui, d'autres marchés ont pris le relais



Dépendance aux bzd et Z-drugs



Merci de votre attention