But if we look closely at the evolution of hematology, the era of personalized medicine began several years ago.

1907: Reuben Ottenberg reports the first known blood compatibility test for transfusion using blood typing techniques and cross-matching between donors and patients to prevent hemolytic transfusion reactions.

1956: The genetic basis for the selective toxicity of fava beans ("favism") and the antimalarial drug primaquine is discovered to be a deficiency in the metabolic enzyme, glucose-6-phosphate dehydrogenase (G6PD).

1977: Cytochrome P450 2D6, a polymorphic metabolizing enzyme, is identified as the culprit for causing some patients to experience an "overdose" or exaggeration of the duration and intensity of the effects of debrisoquine, a drug used for treating hypertension.

Continuing through the years to the present day we can see many examples of personalized therapy that are current practice today: hemopoietic stem cell transplantation, infectious diseases prophylaxis and treatment, GvHD biomarkers, targeted drug levels, pre-emptive therapy on specific molecular targets, integration of targeted therapy inside transplantation program both as bridging therapy and early maintenance post-transplant particularly in acute myeloid leukemia because of the several mutation recognized determining clonal heterogeneity and drug resistance.

Real-world applications of immunotherapy are personalized medicine: allogeneic transplantation a platform for immunotherapy, checkpoint blockade treatments to pick-up anti-leukemia specific responses, CAR-T and TCR engineering, antibodies-redirected anti-leukemia specific responses, suicide-gene engineered T-cells and others.

Gene therapy, gene editing and CAR-T therapy are indubitably additional form of personalized therapy in which patients own cell, appropriately modified, are the therapeutic agent.

As final remark we must recognized limitations of personalized medicine. Several can be listed, in this abstract we wish to underline cost issue. Personalized medicine contributed to the recent rapid and impressive cost increment seriously impacting equity of resources distribution and therapeutic perspectives. As Physicians we should remember what may undoubtedly be the oldest but actual and most relevant definition of personalized medicine: *it's far more important to know what person the disease has than what disease the person has* (Hippocrates).

## New trends in substance abuse during the COVID 19 pandemic

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In order to contain and counteract COVID-19 (COronaVIrus Disease 19), or SARS-CoV-2 acute respiratory disease, people were forced to comply with strict measures such as lockdown and social distancing, changing their lifestyles.

This occurrence had negative consequences on people physical and mental well-being, leading to states of anxiety and anger, sleep disorders depression and post-traumatic stress disorder. This has led more and more individuals to resort to the use of both licit and illicit psychoactive substances, with an increase in alcohol consumption and psychotropic substances, aggravating the conditions of those already suffering from drug addiction [1]. In addition, drugs market had to adapt to the restrictions related to COVID-19, especially after border closures and travel restrictions. The use of human couriers has, more or less, been replaced by smuggling via intermodal containers or via commercial supply chains [2]. Even trade routes have changed, abandoning transit by land in favour of transport by sea, as in the case of the trafficking of cannabis resin produced in Morocco, which was transported by land to the EU via Spain before the pandemic. On the contrary, since the second half of 2020, large seizures of *Cannabis* resin have been reported in several European seaports. The pandemic has also accelerated the digitization of the drug market, replacing street sales with alternative methods that have led consumers to turn to the illegal dark web market or to the use of encrypted messaging services or web platforms such as Telegram or finally to mail services with home delivery. The type of consumed drugs changed, too. Whereas analysis of wastewater, conducted in 2019 indicated an overall increase in consumption of party drugs such as cocaine, MDMA, amphetamine and methamphetamine, drugs usually associated with recreational social events during the pandemic, consumer interest shifted to anxiolytic and narcotic drugs to be consumed in isolation.

In addition to tranquillizers, however, an increasing use of opioids and new synthetic opioids has been reported. In Canada and North America, there has been a net increase in opioid overdose deaths since the start of the pandemic (in Canada, they were 58% higher between April and June 2020 than in the same quarter in 2019). Overdose deaths are mainly attributable to synthetic opioids such as fentanyl [3]. In Europe, little evidence suggested significant changes in the levels of abuse of opioid substitution treatment drugs after the first closure [4]. As well as, signs of increased use of psychedelic and dissociative drugs, such as LSD, 1P-LSD, 2C-B, NBOMes, ketamine, DMT and GHB have emerged. The increase in non-

therapeutic use of benzodiazepines has also raised particular concerns, both because of the low cost and high availability associated with pandemic-related mental health problems. Harm reduction services have reported an increase in benzodiazepines and z drugs use especially among high-risk drug users, prisoners and recreational drug users, often unaware of the content and potency of tablets purchased online.

**References**

(1) Zaami S, Marinelli E, Varì MR. New Trends of Substance Abuse During COVID-19 Pandemic: An International Perspective. Front Psychiatry. 2020 Jul 16;11:700. doi: 10.3389/fpsyt.2020.00700.
(2) EMCDDA – Relazione Europea sulla Droga. Tendenze e Sviluppi 2021. https://www.emcdda.europa.eu/system/files/publications/13838/2021.2256_IT_02_.pdf (last access 12/07/2022).
(3) UNODOC – World Drug Report 2021 (United Nations publication, Sales No. E.21.XI.8). https://www.unodc.org/unodc/en/data-and-analysis/wdr2021.html (last access 12/07/2022).
(4) EMCDDA – Impact of COVID-19 on drug markets, use, harms and drug services in the community and prisons. https://www.emcdda.europa.eu/system/files/publications/13745/TD0321143ENN_002.pdf (last access 12/07/2022).

## Recreational and clinical use of GHB

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γ-hydroxybutyrate (GHB) is an illicit recreational drug of abuse acting as a potent central nervous system depressant and is often encountered during forensic investigations both in living and post-mortem cases. The sodium salt of GHB is registered as a therapeutic agent (Xyrem®), approved in several countries for the treatment of narcolepsy-associated cataplexy and (Alcover®) is an adjuvant medication for detoxification and withdrawal in alcoholics. Small amounts of GHB are produced endogenously (0.5–1.0 mg/L) in various tissues, including the brain, where it functions as both a precursor and a metabolite of the major inhibitory neurotransmitter γ-aminobutyric acid (GABA). Available information indicates that GHB serves as a neurotransmitter or neuromodulator in the GABAergic system, especially via binding to the GABA-B receptor subtype. Although GHB is listed as a controlled substance in many countries abuse still continues, owing to the availability of precursor drugs, γ-butyrolactone (GBL) and 1,4-butanediol (BD), which are often not under control. After ingestion both GBL and BD are rapidly converted into GHB (t½ ~1 min). The Cmax occurs after 20–40 min and GHB is then eliminated from plasma with a half-life of 30–50 min. Only about 1–5% of the dose of GHB is recoverable in urine and the window of detection is relatively short (3–10 h). This calls for expeditious sampling when evidence of drug use and/or abuse is required in forensic casework. The recreational dose of GHB is not easy to estimate and a concentration in plasma of ~100 mg/L produces euphoria and disinhibition, whereas 500 mg/L might cause death from cardiorespiratory depression. Effective antidotes to reverse the sedative and intoxicating effects of GHB do not exist. The poisoned patients require supportive care, vital signs should be monitored and the airways kept clear in case of emesis. After prolonged regular use of GHB tolerance and dependence develop and abrupt cessation of drug use leads to unpleasant withdrawal symptoms. There is no evidence-based protocol available to deal with GHB withdrawal, apart from administering benzodiazepines.

## New synthetic opioids

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In the last decades, several new psychotropic molecules mimicking the pharmacological effect of the classic drugs of abuse appeared on the illegal market, causing acute and fatal intoxications in more than 100 countries worldwide [1]. These molecules are defined as new psychoactive substances (NPSs) by the United Nations Office of Drugs and Crime (UNODC) and their legal status is often controversial, although they pose an increasing public health threat [1]. Recently, the subclass of new synthetic opioids (NSOs), in particular fentanyl and benzoimidazole analogues, stood out as an emerging class among NPSs and raised concerns due to the rapid increase of fatalities related to new analogues [1, 2].