acetylation; miR-1 and -155 target *HDAC4*, promoting myogenesis and impairing transcriptional activity of B-cell lymphoma 6 (*BCL6*); miR-627 and -155 target JMJD1A, decreasing histone demethylation and hypoxic gene expression; miR-132 and -483-5p target *MECP2*, promoting demethylation and cell differentiation.[181] Furthermore, epigenetic drugs reverse epigenetic changes in gene expression and might open new avenues in AD therapeutics. So far, epigenetic drugs (Table 5.5) have only been approved for the treatment of neoplastic processes; most of them are not devoid of severe side effects; and concerns on their capacity to cross the blood–brain barrier and penetrate into the brain may preclude their implantation as potential drug candidates in NDDs.[15,16,170,182]

5.6 Novel Strategies

Patients with NDDs need multifactorial treatments with different drugs of diverse pharmacological profiles. AD patients may take 6–12 different drugs/day for the treatment of dementia-related symptoms, including memory deterioration (conventional anti-dementia drugs, neuroprotectants) (Table 5.1), behavioral changes (antidepressants, neuroleptics, sedatives, hypnotics), and functional decline, or for the treatment of concomitant pathologies (epilepsy, cardiovascular and cerebrovascular disorders, Parkinsonism, hypertension, dyslipidemia, anemia, arthrosis, *etc.*). Over 20% of dementia patients are current users of cardiovascular drugs. A high-throughput screening study assessed 1600 FDA-approved drugs for their ability to modulate Aβ activity; 559 of the 1600 drugs had no effect on APP processing or were toxic to neurons at the concentration tested, while 800 drugs could reduce Aβ content by over 10% in primary neurons derived from Tg2576 mice, among which, 184 drugs were able to reduce Aβ content by more than 30%; 241 drugs could potentially promote Aβ accumulation, including 26 drugs that could increase the level of Aβ by over 30%.[183] The co-administration of several drugs may cause side-effects and adverse drug reactions in over 60% of AD patients, who in 2–10% of the cases require hospitalization. The prevalence of potentially inappropriate medication (PIM) is around 50% in some European cohorts. Cerebral vasodilators are the most widely used class of PIM, accounting for 24.0% of all prescriptions, followed by atropinic drugs and long half-life benzodiazepines. Atropinic drugs were associated with cholinesterase inhibitors in 16% of patients. In over 20% of the patients, behavioral deterioration and psychomotor function can be severely altered by polypharmacy.[184] The principal causes of these iatrogenic effects are the inappropriate combination of drugs, and the genomic background of the patient, responsible for his/her pharmacogenomic outcome.

During the 2002–2012 period, 413 AD trials were performed (124 Phase 1 trials, 206 Phase 2 trials, and 83 Phase 3 trials) (78% sponsored by pharmaceutical companies). Registered trials addressed symptomatic agents (36.6%), disease-modifying small molecules (35.1%) and disease-modifying immunotherapies (18%), with a very high attrition rate (overall success